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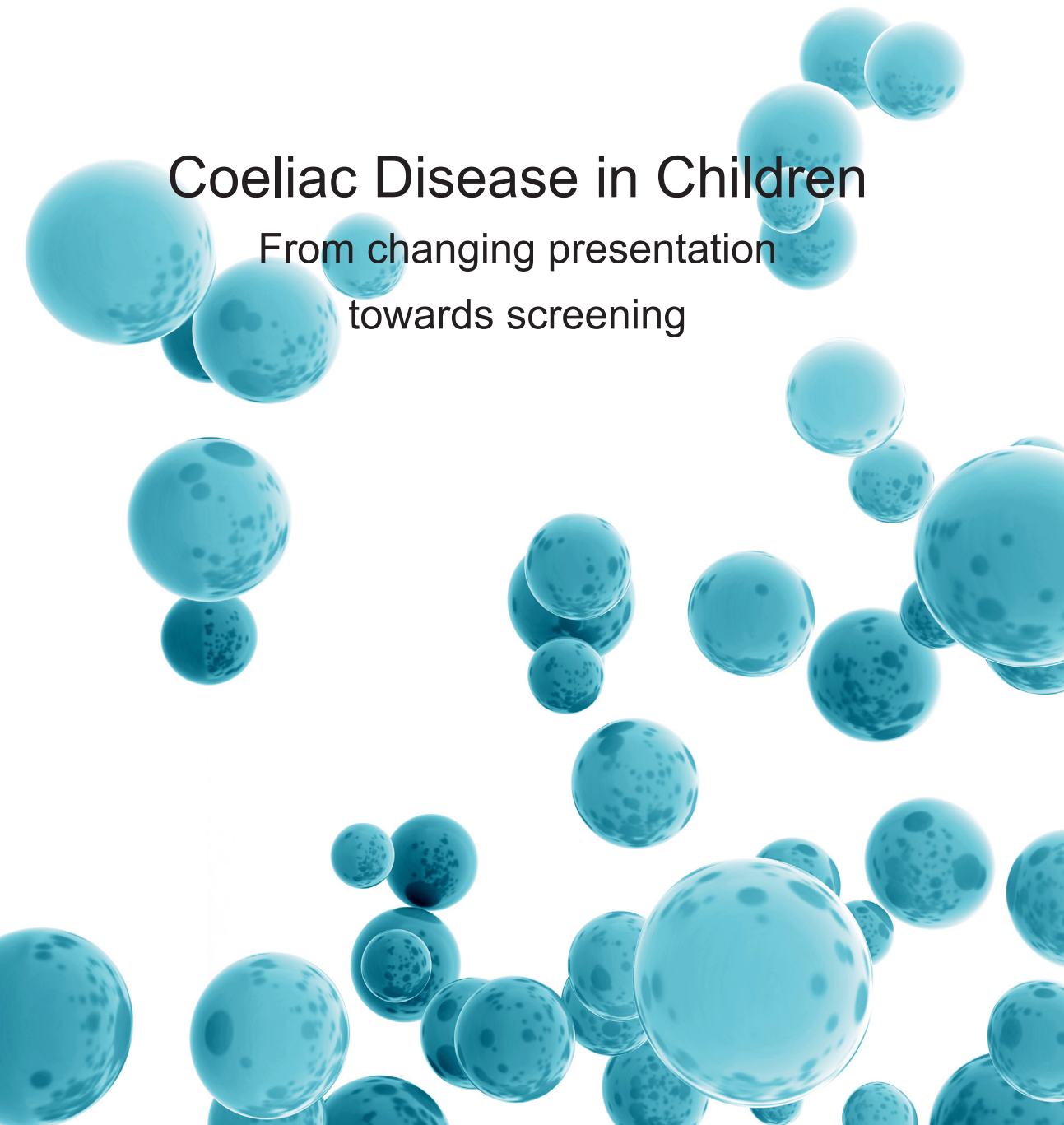
Coeliac Disease in Children

From changing presentation towards screening



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"The important thing is to not stop questioning. Curiosity has its own reason for existing."

Albert Einstein

To my family and friends.

ABSTRACT

Coeliac disease is a life-long immune-mediated disease in which small-bowel mucosal damage and other manifestations of the disease are maintained by dietary gluten in genetically predisposed individuals. The disease may cause variable gastrointestinal and extra-intestinal complaints, but some patients are asymptomatic and can be found only by screening. In recent decades, coeliac disease has become more common and its clinical presentation more diverse. Concurrent changes have been reported in other autoimmune-like disorders, although these shifts may have levelled off in recent years. No similar plateau has been reported in coeliac disease.

Up to 1-3% of the population of developed countries is estimated to suffer from coeliac disease, but despite improved knowledge and better diagnostic methods, the great majority of the patients remain unrecognized. On the other hand, whether coeliac disease should be found and treated in all affected individuals, especially those found by screening, remains controversial. The risk of developing the disease is higher particularly in patients suffering from certain other autoimmune diseases and in close relatives of coeliac disease patients. However, recommendations about screening in risk groups vary because of the limited scientific evidence. It is important to know whether the benefit of screening for coeliac disease exceeds the possible harm.

In some earlier studies, adherence to a gluten-free diet in screen-detected patients is shown to be relatively poor. Furthermore, there is a risk that the diagnosis of life-long disease combined with the demanding dietary treatment causes anxiety and decreases the quality of life, especially in patients who experienced themselves as asymptomatic before their diagnosis. Whether the risk of developing complications is similar in clinically found and screen-detected patients is also unclear.

The present dissertation project is composed of three separate studies. In Study **I**, the aim was to evaluate changes in the clinical presentation of 596 children diagnosed with biopsy-proven coeliac disease in Finland in 1966-2013. Furthermore, we evaluated the secular trends in the clinical incidence of coeliac disease autoimmunity in the twenty-first century in the Pirkanmaa hospital district. In Studies **II** and **III**, we investigated whether children diagnosed by risk-group screening and those found due to clinical suspicion differ at diagnosis (**II-III**), during short-term follow-up (**II**)

and after long-term follow-up in adulthood (**III**) in various disease- and health-related variables. The adult coeliac disease patients in Study **III** were also compared with 110 non-coeliac controls on their health-related quality of life.

Demographic and clinical characteristics, severity of small-bowel damage, coeliac disease antibody levels and other laboratory results and possible concomitant diseases were collected from patient records and in some cases supplemented by interviews (**I-III**). These data were also used to evaluate adherence and response to a gluten-free diet a year after diagnosis (**II**). Currently adult patients answered study questionnaires, which were used to assess their health, lifestyle, success of the dietary treatment and quality of life (**III**).

Study **I** demonstrated that paediatric coeliac disease changed significantly and became milder especially in the 1980s and 1990s, whereas most of the changes reached a plateau in the twenty-first century. The incidence of coeliac disease autoimmunity rose until 2007, but thereafter seemed to fluctuate without a clear trend. Up to one-third of all patients diagnosed in the 2000s were found due to at-risk screening.

In Study **II**, we saw that also patients found by risk-group screening (n=145) often suffered from previously unrecognized symptoms, anaemia and poor growth, although to a lesser degree than did clinically detected patients (n=359). The severity of histological damage required for the diagnosis and the levels of coeliac disease antibodies at diagnosis, as well as dietary adherence and treatment response a year after diagnosis, were comparable among these groups (**II**).

Study **III** showed that the 48 patients found by risk-group screening in childhood did not differ from the 188 clinically found patients in adulthood, on average 19 years after diagnosis. The groups were comparable in their dietary adherence, most aspects of quality of life and lifestyle, and their experiences with the disease and its treatment. However, originally asymptomatic screen-detected patients reported more current anxiety compared with others, and coeliac disease patients had an overall poorer vitality compared with healthy controls.

Results of the present study clarify the changes in the clinical presentation of coeliac disease during this long time period in the same area. In the future, this may help in deciphering whether environmental factors play a role in the pathogenesis and clinical presentation of the disease. Furthermore, the observed advanced histological damage at diagnosis, together with successful dietary treatment and a good long-term prognosis for screened, even asymptomatic, patients, supports active screening for coeliac disease among at-risk children.

TIIVISTELMÄ

Keliakia on elinikäinen, immuunivälitteinen sairaus, jossa ravinnon gluteeni ylläpitää ohutsuolen limakalvovauriota ja muita keliakian ilmentymiä geneettisesti alttiilla henkilöillä. Keliakia voi aiheuttaa ruuansulatuskanavan tai suoliston ulkopuolisia oireita, mutta osa potilaista on täysin oireettomia ja heidät voidaan löytää vain riskiryhmäseulontojen avulla. Viime vuosikymmenten aikana keliakia on yleistynyt merkittävästi ja taudinkuva on muuttunut monipuolisemmaksi. Muutoksia on tapahtunut samanaikaisesti myös muissa autoimmuunisairauksissa, mutta viime vuosina ne vaikuttaisivat tasaantuneen. Keliakiaan liittyen samanlaista ilmiötä ei ole raportoitu.

Jopa 1-3 % väestöstä ympäri maailman sairastaa keliakiaa, mutta vaikka keliakiatietämys on nykyään monissa maissa hyvällä tasolla, suurin osa potilaista on ilman diagnoosia. Toisaalta on osin epäselvää, keneltä keliakiaa pitäisi etsiä ja hoitaa. Keliakiariskin tiedetään olevan kohonnut eräitä muita autoimmuunisairauksia sairastavilla potilailla ja keliakiapotilaiden lähisukulaisilla, joiden kohdalla suositukset keliakian seulomisesta ovat kuitenkin vaihtelevia puutteellisen tieteellisen näytön vuoksi. Olisi tärkeää tietää, ovatko seulomalla löydettyjen potilaiden hoidosta saamat hyödyt suurempia kuin haitat.

Aiemmissa tutkimuksissa on saatu vaihtelevia tuloksia seulomalla löydettyjen potilaiden sitoutumisesta keliakian hoitona olevaan gluteenittomaan ruokavalioon. Riskinä on, että pitkäaikaissairauden diagnoosi ja tiukan ruokavalion noudattaminen aiheuttavat ahdistusta ja heikentävät elämänlaatua erityisesti, jos potilas on kokenut itsensä oireettomaksi ennen keliakiadiagnoosia. Lisäksi ei tiedetä, onko oireettomien potilaiden riski kehittää keliakian vakavia komplikaatioita yhtä suuri kuin oireisilla potilailla, ja voidaanko keliakiaseulonnalla ja varhaisella hoidon aloittamisella vaikuttaa esimerkiksi liitännäissairauksien ilmaantumiseen.

Väitöskirja koostuu kolmesta erillisestä osatyöstä. Osatyössä **I** oli tavoitteena selvittää keliakian taudinkuvan muutoksia 596 keliakiadiagnoosin Suomessa saaneella lapsella vuosien 1966-2013 aikana sekä tutkia, onko keliakian autoimmuniteetin kliininen ilmaantuvuus lapsilla muuttunut 2000-luvulla Pirkanmaan sairaanhoitopiirin alueella (**I**). Osatöissä **II** ja **III** selvitettiin, eroavatko riskiryhmäseulonnoissa löytyneet lapsipotilaat niistä, joilla on epäilty keliakiaa

oireiden tai löydösten vuoksi diagnoosihetkellä (**II-III**), noin vuoden kuluttua diagnoosista (**II**) tai aikuisena (**III**). Aikuisia keliakiapotilaita vertailtiin elämänlaadun kokemisen suhteen myös 110 terveeseen kontrolliin (**III**).

Potilaskertomusteksteistä ja osittain haastatteluiden avulla kerättiin tiedot kliinisistä ominaisuuksista, suolistovaurion vaikeusasteesta, keliakiavasta-ainetasoista ja muista laboratoriokokeiden tuloksista sekä mahdollisista liitännäissairauksista diagnoosihetkellä (**I-III**). Lisäksi näiden avulla selvitettiin ruokavaliohoidon onnistumista ja hoitovastetta noin vuosi diagnoosin jälkeen (**II**). Nykyään aikuiset potilaat vastasivat tutkimuskyselyihin, joiden avulla selvitettiin muun muassa yleistä terveydentilaa ja elämäntyyliä, ruokavaliohoidon onnistumista ja elämänlaatua (**III**).

Osatyön **I** tulokset osoittivat keliakian taudinkuvan voimakkaan muuttumisen ja lieventymisen etenkin 1980-1990-luvuilla, sekä suurimman osan muutoksista tasaantumisen 2000-luvulla. Keliakian ilmaantuvuus kasvoi 2000-luvun alussa, mutta vaikutti sen jälkeen tasaantuneen. Jopa kolmasosa potilaista löydettiin riskiryhmäseulontojen avulla.

Osatyössä **II** nähtiin myös riskiryhmäseulonnoissa löydettyjen lasten (n=145) kärsivän aiemmin tunnistamattomista oireista, anemiasta ja heikentyneestä kasvusta, vaikkakin harvemmin kuin kliinisen epäilyn vuoksi löydetyt (n=359). Keliakian vaikeusaste diagnoosihetkellä sekä gluteenittoman ruokavalion onnistuminen ja siitä hyötyminen noin vuosi diagnoosin jälkeen olivat verrattavissa ryhmien välillä.

Osatyössä **III** osoitettiin riskiryhmäseulonnoissa löytyneiden 48 potilaan olevan verrattavissa kliinisen epäilyn vuoksi diagnosoituihin 188 potilaaseen myös aikuisena, keskimäärin 19 vuoden kuluttua diagnoosista. He noudattivat ruokavaliohoitoa yhtä hyvin, eikä ryhmien välillä ollut eroa suurimmassa osassa elämänlaatua tai elämäntyyliä selvittävissä kysymyksissä, tai sairauden kokemisessa. Verrokit raportoivat energisyyden olevan parempi kuin keliakiapotilailla, ja seulomalla löydetyillä alun perin oireettomilla potilailla oli enemmän ahdistusta kuin muilla.

Väitöskirjatyön tulokset selventävät keliakian taudinkuvan muutoksia pitkällä aikavälillä samalla alueella, jonka avulla voidaan jatkossa selvittää keliakian syntyyn ja taudinkuvan luonteeseen mahdollisesti vaikuttavia ympäristötekijöitä. Myös seulomalla löytyneillä potilailla oli diagnoosihetkellä merkittävä suolistovaurio, jonka lisäksi he sitoutuivat hyvin ruokavaliohoitoon pitkällä aikavälillä eikä se vaikuttanut heikentävän heidän elämänlaatuaan. Nämä löydökset tukevat keliakian riskiryhmiin kuuluvien lasten aktiivisempaa seulontaa.

TABLE OF CONTENTS

ABBREVIATIONS

ACG	American College of Gastroenterology
AGA	anti-gliadin antibody
AIT	autoimmune thyroidal disease
ALD	autoimmune liver disease
ARA	anti-reticulin antibody
BMD	bone mineral density
BMI	body mass index
BSPGHAN	British Society for Paediatric Gastroenterology, Hepatology and Nutrition
Dg	diagnosis
DIPP	Diabetes Prediction and Prevention
ELISA	enzyme-linked immunosorbent assay
EmA	endomysial antibody
ESPGHAN	European Society for Paediatric Gastroenterology Hepatology and Nutrition
GSRS	Gastrointestinal Symptom Rating Scale
Hb	blood haemoglobin
HbA1c	glycated blood haemoglobin
HLA	human leukocyte antigen
ICD	International Statistical Classification of Diseases and Related Health Problems
IFA	indirect immunofluorescence assay
Ig	immunoglobulin
IQR	interquartile range
NASPGHAN	North American Society for Pediatric Gastroenterology, Hepatology and Nutrition
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
ND	no data
MCV	erythrocyte mean corpuscular volume
PGWB	Psychological General Well-Being questionnaire

PTH	para-thyroid hormone
Rf	reference value
SD	standard deviation
SPSS	Statistical Package for the Social Sciences
TEDDY	The Environmental Determinants of Diabetes in the Young
TG	transglutaminase
tTG	tissue transglutaminase
tTGab	tissue transglutaminase antibody
T1D	type 1 diabetes
USPSTF	US Preventive Services Task Force

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred in the text by the Roman numerals **I-III**.

I Kivelä L, Kaukinen K, Lähdeaho M-L, Huhtala H, Ashorn M, Ruuska T, Hiltunen P, Visakorpi J, Mäki M and Kurppa K (2015): Presentation of coeliac disease in Finnish children is no longer changing: a 50-year perspective. Journal of Pediatrics. 167:1109-15.e1.

II Kivelä L, Kaukinen K, Huhtala H, Lähdeaho M-L, Mäki M and Kurppa K (2017): At-risk screened children with coeliac disease are comparable in disease severity and dietary adherence to those found because of clinical suspicion: a large cohort study. Journal of Pediatrics. 183:115-21.e2.

III Kivelä L, Popp A, Arvola T, Huhtala H, Kaukinen K and Kurppa K (2018): Long-term health and treatment outcomes in adult coeliac disease patients diagnosed by screening in childhood. United European Gastroenterology Journal. 6:1022-31.

INTRODUCTION

Coeliac disease is a chronic, immune-mediated disease in which dietary gluten drives damage to the small intestine and other organs in genetically susceptive individuals (Ludvigsson et al. 2013). When coeliac disease is suspected because of symptoms or findings or in subjects belonging to a high-risk group, the diagnostic pathway usually begins by measuring disease-specific autoantibodies. Then it proceeds to small-bowel biopsy, where mucosal villous atrophy in histological analysis verifies the diagnosis (Husby et al. 2012, Ludvigsson et al. 2014). However, according to the most recent European guidelines, the intestinal biopsy can be omitted in symptomatic children with correct genetics and high positive coeliac disease antibodies as defined in greater detail in the criteria (Husby et al. 2012). Treatment for coeliac disease is a lifelong and strict avoidance of dietary gluten, which in most cases results in an alleviation of symptoms, gradual improvement of mucosal damage and decrease in serum antibodies (Kaukinen et al. 2010). However, whether also apparently asymptomatic patients benefit from the treatment has been an issue of controversy due to insufficient scientific evidence (Ludvigsson et al. 2015, Chou et al. 2017).

During recent decades, coeliac disease has become one of the most common food-related chronic diseases, affecting up to 1-3% of population, although the majority are as yet undiagnosed (Singh et al. 2018). Along with this increasing incidence, its clinical presentation has changed significantly, from a rare malabsorption syndrome of infants to a multifaceted condition affecting all ages (McGowan et al. 2009, Roma et al. 2009, Whyte and Jenkins 2013). Different symptoms and findings of coeliac disease include both gastrointestinal complaints such as abdominal pain, diarrhoea and constipation and extra-intestinal manifestations including dermatological, neurological and psychological symptoms, arthralgia, impaired growth and laboratory abnormalities. Although the changes in the clinical features were reported as early as the 1980s (Mäki et al. 1988), the exact changes in clinical presentation over this lengthy course of time and the trends during the twenty-first century remain unclear. Interestingly, changes have also been reported in some other autoimmune-type diseases such as type 1 diabetes and inflammatory bowel disease (Harjutsalo et al. 2008, Martín-de-Carpi et al. 2014),

although they might be already levelling off (Berhan et al. 2011, Agnarsson et al. 2013, Harjutsalo et al. 2013, Henriksen et al. 2015).

In the 2000s, coeliac disease patients were increasingly found by improved diagnostic methods and lower threshold case-finding, but, despite this, most of them remain unrecognized (Mustalahti et al. 2010). The diagnostic yield could still be improved and even asymptomatic patients found by screening, which could be focused on risk groups such as family members of coeliac disease patients and those with concomitant autoimmune diseases (Ludvigsson et al. 2015). However, whether this approach should be applied and to what extent remains unanswered (Chou et al. 2017). There is scarce evidence about the pros and cons of the screening, especially concerning the long-term prognosis and adherence to the dietary treatment.

The aim of this dissertation project was first to evaluate changes in clinical presentation in children diagnosed with coeliac disease in Finland from the 1960s to the present, and then to focus on those patients found by risk-group screening. To elucidate the possible benefits and harms of screening, we compared screen-detected paediatric patients to clinically found patients at the time of diagnosis, after short-term follow-up and after long-term follow-up extending into adulthood.

REVIEW OF THE LITERATURE

1 AETIOLOGY AND PATHOGENESIS OF COELIAC DISEASE

Coeliac disease is a lifelong condition in which dietary gluten drives immune dysregulation, resulting in inflammation and structural damage of the small-bowel mucosa and causing manifestations also in other organs (Ludvigsson et al. 2013). Development of the disease requires a genetic predisposition and ongoing consumption of dietary gluten. However, the combination of these factors does not fully explain the variable disease onset, and further triggers have been sought from environmental factors (Kupfer and Jabri 2012).

1.1 Genetics

The genetic association of coeliac disease with certain human leukocyte antigen (HLA) types was recognized as early as more than 40 years ago (Stokes et al. 1972). Thereafter, epidemiologic studies and the development of genetic techniques have provided more support for the importance of genetic factors in the pathogenesis of the disease (Wolters and Wijmenga 2008).

HLA-DQ is a class II cell surface receptor (αβ-heterodimer) located on antigen-presenting cells, and its function is to bind and present peptides to immune cells. HLA-DQ is encoded by HLA-DQA1 and -DQB1 genes on chromosome 6p21.3, and the configuration of these alleles determines the risk of coeliac disease and may also affect its clinical presentation (Sollid et al. 1989, Zubillaga et al. 2002, Megiorni et al. 2009).

More than 90% of coeliac disease patients carry HLA-DQ2 (DQA1*05-DQB1*02) and most of the remaining HLA-DQ8 (DQA1*03:01-DQB1*03:02) (Wolters and Wijmenga 2008, Kupfer and Jabri 2012). In a European study, only 0.4% of coeliac disease patients were both HLA-DQ2 and -DQ8 negative, demonstrating how rare the disease is in this patient group (Karell et al. 2003). The most common HLA configuration in coeliac disease patients is DQB1*02/DQA1*05 heterozygosity, which is found approximately in 50% of patients (Megiorni et al. 2009). Patients with DQB1*02 homozygosity have the

highest risk of developing coeliac disease, and they may also suffer from a more severe presentation with a younger age at disease onset (Zubillaga et al. 2002, van Belzen et al. 2004, Biagi et al. 2012).

Although 25-30% of the European population are HLA-DQ2 positive, only approximately 4% of them will develop coeliac disease (Sollid et al. 1989, Polvi et al. 1996). HLA-DQ2 or -DQ8 positivity is thus necessary but not sufficient to cause coeliac disease, and it is estimated to explain 40% of the genetic variance in the disease (Trynka et al. 2011). Genetic factors explaining the remaining risk have been proposed to be found in different non-HLA regions (Sharma et al. 2016). Genome-wide association studies have identified non-HLA loci whose coeliac disease-associated genes are involved also in other autoimmune disorders and adaptive and innate immunity (Dubois et al. 2010, Trynka et al. 2011). However, these non-HLA genes do not explain all of the remaining risk of developing coeliac disease, and interactions between different genes and environmental factors and some rare genetic variants could also play a role in its aetiology (Kupfer and Jabri 2012).

1.2 Gluten and immune dysregulation

Gluten is a storage protein in cereals and consists of ethanol-insoluble glutenins and ethanol-soluble prolamines. Prolamines in wheat (α-, β- and γ-gliadins), rye (secalines) and barley (hordeins) are rich in glutamine and proline peptide sequences, which are poorly digested in the gastrointestinal tract (Shewry and Tatham 1990). It has been speculated that if small-bowel mucosal permeability is for some reason increased, these undigested fractions are able to enter through the epithelial barrier to the lamina propria (Heyman et al. 2012).

In the lamina propria, gluten peptides are deaminated by calcium-dependent tissue transglutaminase (tTG) enzyme, which is released from the cells during inflammation. The tTG catalyses the modification of the peptides to more immunogenic molecules, which then promote an inflammatory reaction (Di Sabatino et al. 2012). Deaminated gluten peptides activate an innate immune response by increasing the expression of interleukin-15 in the intestinal epithelium and result in the transformation of intraepithelial lymphocytes into cytotoxic cells (Korneychuk et al. 2014). Gliadin fractions stimulate also the adaptive immune system by binding to antigen-presenting cells which express HLA-DQ2 and/or -DQ8 on their surface. Gliadin-specific CD4+ T cells recognize these structures and produce inflammatory cytokines, especially interferon-γ. These cytokines cause

tissue damage and activate B cells to produce autoantibodies against tTG (tTGab), which is thus also an autoantigen in the immune response (Di Sabatino et al. 2012). Furthermore, tTGab may play a direct role in the pathogenesis (Caja et al. 2011). The above-mentioned processes result in the inflammation and gradual structural destruction of small-bowel mucosa and also damage other organ systems (Kupfer and Jabri 2012).

1.3 Other environmental factors

The development of coeliac disease is not completely explained by current knowledge about genetics and the consumption of gluten. The role of environmental factors as a trigger for the loss of immune tolerance to gluten is supported by epidemiologic studies, which have reported rapid changes in the true prevalence and clinical presentation of coeliac disease over time and between closely located geographic areas (Ivarsson et al. 2000, Lohi et al. 2007, Kondrashova et al. 2008, Roma et al. 2009, White et al. 2013a). Concurrent changes in hygienic environment and its differences between countries have been proposed to explain some of the changes (Kondrashova et al. 2008). Furthermore, in recent years, the significance of the microbiota (Cenit et al. 2015) and a variety of other environmental factors have also been studied to determine their possible role in coeliac disease pathogenesis.

On the basis of several prospective follow-up studies, gluten is currently recommended to be introduced in the diet at between four and 12 months of age, and large amounts of gluten should be avoided during infancy, whereas the continuation of breastfeeding seems not to alter the risk of developing coeliac disease (Størdal et al. 2013, Vriezinga et al. 2014, Lionetti et al. 2014, Jansen et al. 2014, Aronsson et al. 2015, Aronsson et al. 2016, Szajewska et al. 2016). Also, viral infections and the use of antibiotics during early life, as well as perinatal and maternal factors, could play a role in its pathogenesis (Mårild et al. 2012, Canova et al. 2014, Kemppainen et al. 2017a, Kemppainen et al. 2017b). However, more evidence about the role of these factors in the development of coeliac disease is, certainly, needed.

2 EPIDEMIOLOGY OF COELIAC DISEASE

Coeliac disease is currently known to be one of the most common food-related chronic disorders, although the majority of patients remain unrecognized (**Table 1**). Therefore, it is important to distinguish between the true and the clinical prevalence of the condition. True prevalence can be estimated by population-based screening studies, whereas clinical prevalence relies on case-finding.

The estimated true prevalence of coeliac disease varies between 0.2% and 5.6% and clinical prevalence from non-existent to 0.9% (**Table 1**). So far, the highest population-based prevalence of coeliac disease has been reported in Saharawi children (Catassi et al. 1999) and in Sweden (Myléus et al. 2009), and the lowest in Japan (Fukunaga et al. 2018). These findings could be explained by differences in genetic background and gluten consumption (Catassi et al. 1999, Myléus et al. 2009, Fukunaga et al. 2018).

Apart from differences between countries, prevalence of the disease has been reported to differ significantly even within the same country, for example in India, where the use of gluten and genetic background varies considerably from region to region (Ramakrishna et al. 2016), but also in Finland and the United Kingdom, where the finding is likely explained mostly by varying diagnostic activity (Virta et al. 2009, West et al. 2014).

One prospective follow-up study found that coeliac disease antibodies most likely appear during the first three years of life in genetically susceptible children (Hagopian et al. 2017). However, coeliac disease and especially its clinical symptoms can develop at any age, and new diagnoses have been reported also in the elderly (Vilppula et al. 2009). This explains why the reported true prevalence figures often increase when the evaluation of population is extended from children to include adults as well (**Table 1**).

Table 1. Examples of clinical and estimated true population-based prevalence of coeliac disease in different age groups, countries and time periods.

Country	Study period	Screened patients	Diagnostic criteria	Prevalence, %		Reference
				Clinical	True [a]	
Algeria	1998	989 children	EmA	0	5.6	Catassi et al. 1999
Argentina	2008-2009	2,219 children	biopsy	0.32	1.3	Mora et al. 2012
Australia	1994-1995	3,011 adults	biopsy [b]	ND	0.6	Chin et al. 2009
Finland	1978-1980	6,993 adults	tTGab + EmA	0.03	1.1	Lohi et al. 2007
	1994	3,654 children	biopsy	0.27	1.0	Mäki et al. 2003
	2000-2001	6,402 adults	tTGab + EmA	0.50	2.0	Lohi et al. 2007
	2002	2,815 elderly	biopsy	0.89	2.1	Vilppula et al. 2008
	2005	2,216 elderly	biopsy	ND	2.3	Vilppula et al. 2009
Germany	1989-1990	4,633 adults	tTGab + EmA or biopsy	0	0.2	Mustalahti et al. 2010
	1999-2001	4,173 adults	tTGab + EmA or biopsy	0.02	0.3	Mustalahti et al. 2010
	2003-2006	12,741 children	tTGab	0.07	0.8	Laass et al. 2015
Hungary	ND	427 children	biopsy	ND	1.2	Korponay-Szabó et al. 1999
	2005	2,690 children	biopsy	0.19	1.4	Korponay-Szabó et al. 2007
India	2008-2009	3,643 children	biopsy	ND	1.4 [c]	Makharia et al. 2011
	2008-2009	6,845 adults	biopsy	ND	0.9 [c]	Makharia et al. 2011
Italy	1997-2000	2,645 children	tTGab + EmA or biopsy	0	1.1	Mustalahti et al. 2010
	1999-2000	3,188 children	biopsy [d]	0.06	1.1	Tommasini et al. 2004
	2000-2002	4,781 adults	tTGab + EmA or biopsy	0.02	0.7	Mustalahti et al. 2010
	2003	1,002 adolescents and adults	biopsy	0.04	1.0	Menardo et al. 2006
Japan	2014-2016	2,055 adults	biopsy	0	0.1	Fukunaga et al. 2018

Netherlands	1987-1997	50,760 adults	tTGab + EmA + HLA	0.02 [e]	0.4	Schweizer et al. 2004
	1997-1998	6,127 children	biopsy	0.04	0.5	Csizmadia et al. 1999
New Zealand	1996	1,064 adults	biopsy	0.30	1.2	Cook et al. 2000
Russia	1997-2001	1,988 children	biopsy	0.05	0.2	Kondrashova et al. 2008
Spain	1998-1999	484 children	biopsy	ND	0.9	Castano et al. 2004
Sweden	1994	1,894 adults	biopsy	0.11	0.5	Ivarsson et al. 1999
	1994-1995	690 children	biopsy [f]	0.73	2.0	Carlsson et al. 2001
	2005	7,567 children	biopsy	0.89	2.9	Myleus et al. 2009
Tunisia	2003-2004	6,284 children	tTGab + EmA or biopsy	0.03	0.6	Ben Hariz et al. 2007
Turkey	2006-2008	20,190 children	tTGab + EmA or biopsy	0.96 [e]	1.7	Dalgic et al. 2011
UK	1986-1987	4,656 adults	tTGab + EmA or biopsy	0.28	1.5	Mustalahti et al. 2010
	1990-1995	7,550 adults	EmA	0.05	1.2	West et al. 2003
	2000	1,975 children	tTGab + EmA or biopsy	0.05	0.9	Mustalahti et al. 2010
USA	1995-2001	16,847 elderly	tTGab + EmA	0.20	1.0	Godfrey et al. 2010
	2009-2010	7,798 adults	tTGab + EmA	0.08 [e]	0.7	Rubio-Tapia et al. 2012
	2006-2011	30,425 adults	tTGab + EmA	ND	1.1	Choung et al. 2017

[a] Estimated based on population screening.
[b] In the absence of biopsy: elevated tTGab in three samples + suitable HLA.
[c] Patients suffering from clinical features of coeliac disease and 10% of those without clinical suspicion were screened.
[d] In the absence of biopsy: tTGab + EmA + suitable HLA.
[e] Self-reported diagnosis.
[f] If biopsy was omitted, diagnosis was made based on elevated antigliadin + EmA + positive response to a gluten-free diet.
Abbreviations: EmA: endomysial antibody; HLA: human leukocyte antigen; ND: no data; tTGab: tissue transglutaminase antibody.

2.1 Temporal changes

The clinical incidence of coeliac disease has increased significantly in recent decades, especially due to improved diagnostic methods and better knowledge of the condition (**Figure 1** and Ress et al. 2012, West et al. 2014, Beitnes et al. 2016, Almallouhi et al. 2017). Sensitive and specific coeliac disease antibodies have enabled a simplified screening evaluation of the disease by blood sample from the 1980s-1990s when they were found (Chapter 3.1). Consequently, a wide clinical presentation as well as asymptomatic patients and specific risk groups have been increasingly identified (Chapter 6.1). However, also the true prevalence of the disease seems to be rising (**Table 1**), which is possibly explained by some as-yet unrecognized environmental factors (Chapter 1.3).

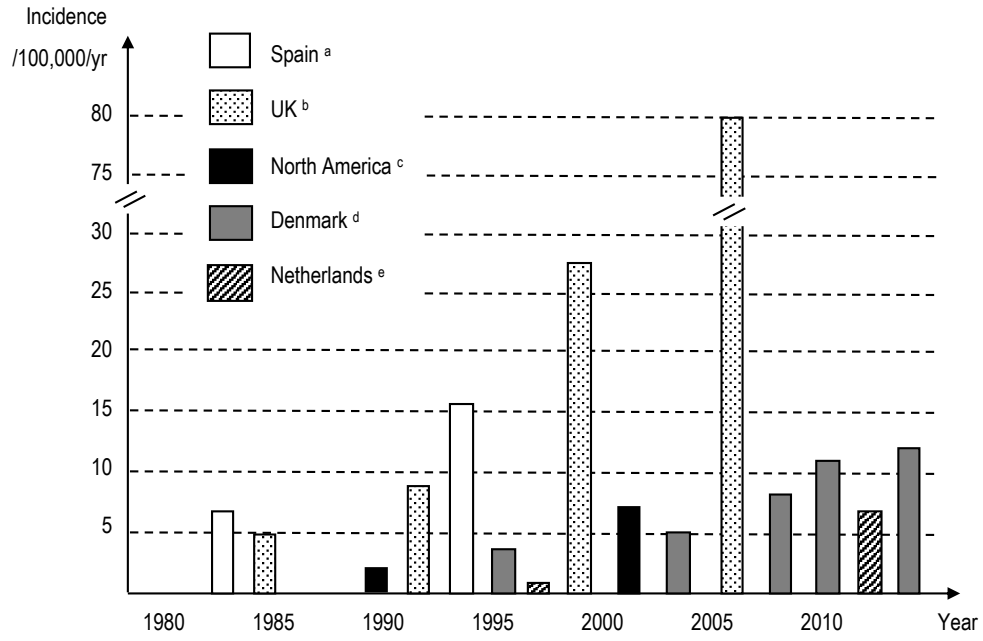

Figure 1. Changes in clinical incidence of paediatric coeliac disease over time and in different countries. Data collected from the following studies: [a] López-Rodríguez et al. 2003; [b] Whyte et al. 2013; [c] McGowan et al. 2009; [d] Dydensborg et al. 2012; and [e] Burger et al. 2014.

Concurrently with coeliac disease, the incidence and prevalence of many other immune-mediated diseases such as inflammatory bowel diseases, type 1 diabetes, asthma and allergies have increased (Harjutsalo et al. 2008, Hansen et al. 2013, Martín-de-Carpi et al. 2014). Simultaneous changes in these diseases support the possible role of environmental factors (Okada et al. 2010). However, in contrast to coeliac disease, there have been some reports of a plateau in the changes of these other diseases after the 1990s, for example in Sweden, Finland and Iceland, (Berhan et al. 2011, Agnarsson et al. 2013, Harjutsalo et al. 2013, Henriksen et al. 2015), despite the incidence of inflammatory bowel disease, which is still increasing in Finland (Virta et al. 2017).

2.2 High-risk groups and comorbidities

The prevalence of coeliac disease is higher than in the normal population particularly among the relatives of coeliac disease patients and in those suffering from certain other immune-mediated disorders and chromosomal abnormalities (Bonamico et al. 2001, Rubio-Tapia et al. 2008, Nadeem and Roche 2013, Roy et al. 2016, Craig et al. 2017). This is likely mostly explained by shared genetic factors (Megiorni et al. 2009, Bratanic et al. 2010, Lundin and Wijmenga 2015) as opposed to, for example, environmental factors.

Coeliac disease has been reported to affect 2-38% of first-degree relatives of patients; the pooled prevalence based on recent meta-analysis is 8% (Singh et al. 2015). The same meta-analysis reported a pooled prevalence for second-degree relatives to be 2%. However, the difficulty with these numbers lies in the wide variety in the prevalence of coeliac disease in general (**Table 1**), which hampers a comparison of the true differences between studies and countries. The risk of developing coeliac disease is highest among monozygotic twins, in whom prevalence has been reported to be up to 75-80% (Kuja-Halkola et al. 2016). Siblings seem to have the greatest risk of family members overall of developing coeliac disease, followed by offspring and then mothers and fathers (Singh et al. 2015).

Besides family members, the most studied high-risk group for coeliac disease is patients suffering from type 1 diabetes. The prevalence of coexisting coeliac disease in children and adolescents with type 1 diabetes varies between 4.8% and 9.3% (Kurppa et al. 2017), and coeliac disease patients also have a greater risk of developing type 1 diabetes (Ludvigsson et al. 2006). Unlike coeliac disease, type 1 diabetes is connected more strongly to HLA-DQ8, and patients with HLA-

DQ2/DQ8 heterozygosity have the highest risk of developing the disease (Liu et al. 2014, Viken et al. 2017). In addition to HLA-DQ2 and -DQ8, coeliac disease and type 1 diabetes share common non-HLA genetic risk factors (Smyth et al. 2008, Bratanic et al. 2010).

Patients suffering autoimmune thyroidal diseases have also been described as having a substantially increased risk of developing coeliac disease, and prevalences of up to 7.6% have been reported (Larizza et al. 2001). In a recent meta-analysis, the pooled prevalence of coeliac disease among patients with autoimmune thyroid disease was only 1.6%, but the heterogeneity between studies was large and the numbers varied, for example between different age groups (Roy et al. 2016). Similar to patients with type 1 diabetes, also coeliac disease patients are at risk of developing thyroidal diseases (Canova et al. 2016). Other high-risk groups for coeliac disease are especially patients with Down's syndrome, in whom the prevalence of coeliac disease has been reported to be up to 18.6% (Pavlovic et al. 2017), and patients with Turner's syndrome (9.4%) (Gillett et al. 2000; Nadeem and Roche 2013).

There are also other conditions associated to coeliac disease, but, compared with above-described high-risk groups, the true risk of coeliac disease in these groups is not unambiguous. There is a probable association between coeliac disease and William's syndrome, Sjögren's syndrome, Addison's disease, selective IgA deficiency, IgA glomerulonephritis and autoimmune liver disorders such as autoimmune hepatitis (Meini et al. 1996, Iltanen et al. 1999, Myhre et al. 2003, Di Biase et al. 2009, Stagi et al. 2014, van Gerven et al. 2014, Nurmi et al. 2018), whereas there are occasional reports about coeliac disease and primary biliary cirrhosis, alopecia areata and sarcoidosis (Corazza et al. 1995, Bardella et al. 1997, Hwang et al. 2008). Asthma, atopy, migraine, rheumatoid arthritis and inflammatory bowel diseases have presented together with coeliac disease, probably in coincidence (Canova et al. 2015, Lerner and Matthias 2015, Assa et al. 2017).

Associated diseases occur often together with coeliac disease, but by definition cannot be treated or prevented with a gluten-free diet, which distinguishes them from manifestations of coeliac disease. However, it has been debated whether an early-initiated gluten-free diet could reduce also the risk of developing coexisting autoimmune diseases in coeliac disease patients (Ventura et al. 1999, Sategna Guidetti et al. 2001).

3 DIAGNOSTICS OF COELIAC DISEASE

Coeliac disease-specific antibodies, particularly tTGab and endomysial antibodies (EmAs), are used as the first line of screening tests when suspicion of the disease has been roused. Furthermore, a once-in-a-lifetime measurement of total immunoglobulin (Ig) A is often recommended to exclude selective IgA deficiency, which is 10-20 times more common in coeliac disease patients than in the normal population (Meini et al. 1996, Chow et al. 2012). If they test positive for coeliac disease antibodies, patients are usually referred to gastro-duodenoscopy, and small-bowel mucosal biopsies are obtained to confirm the diagnosis (Husby et al. 2012, Ludvigsson et al. 2014).

The gold standard for coeliac disease diagnosis has long been histologically confirmed villous atrophy and crypt hyperplasia in the biopsy sample. However, the most recent European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guidelines allow diagnosis in children without intestinal biopsy if the patient has typical symptoms, tTGab levels ten times the cut-off value, positive EmA results on a separate occasion and positive HLA-DQ2 and/or HLA-DQ8 results (Husby et al. 2012). Recently, HLA analysis was reported not to increase the accuracy of the diagnosis, indicating that it could be omitted in routine evaluations (Werkstetter et al. 2017). Furthermore, although the serological diagnosis is currently not recommended in asymptomatic patients, recent studies suggest that it would be reliable also in them (Trovato et al. 2015, Paul et al. 2018). In dermatitis herpetiformis, the cutaneous manifestation of coeliac disease (Chapter 6.2), the diagnosis is confirmed from a skin biopsy of healthy skin area next to the lesion by detecting characteristic IgA deposits in immunological staining. In patients with dermatitis herpetiformis, a gastro-duodenoscopy is recommended for those over 40 years old and/or suffering gastrointestinal symptoms (Collin et al. 2017). In other adult patients, and for example in Finland also in all paediatric patients, diagnosis still relies on villous atrophy (Coeliac disease, Current Care Guidelines 2010, Ludvigsson et al. 2014).

3.1 Serological tests

The same antibodies relevant in the pathogenesis can often be used in diagnostics to describe the adaptive immune response by measuring the antibodies from blood samples or tissue biopsies. Mucosal type IgA antibodies are the most accurate in coeliac disease and therefore the main antibodies used in the diagnostics, except in patients with IgA deficiency, of whom only IgG-type coeliac antibodies can be measured (Korponay-Szabó et al. 2003).

The first autoantibodies with a true relevance in coeliac disease were anti-reticuline antibodies (ARAs), which are directed against the reticular fibres of the endomysium, the soft tissue covering smooth muscle fibres (Seah et al. 1971). Although there are some problematic aspects of ARA testing, it was widely used before the modern antibody tests due to its good sensitivity and specificity (Mäki et al. 1984, Mäki 1995). Also, anti-gliadin antibodies (AGAs) were previously used to detect antibodies against the gliadin part of gluten (O'Farrelly et al. 1983). These antibodies are relatively easy to measure using automated enzyme-linked immunosorbent assay (ELISA), but their sensitivity and specificity are heterogeneous (Hill 2005a). AGAs have also been found in healthy individuals and in disorders other than coeliac disease (Mäki 1995). Consequently, their usefulness in diagnostics is limited, despite patients suffering from gluten ataxia (Hadjivassiliou et al. 2002).

Antibodies against the endomysial structure of smooth muscle bundles (EmAs) resemble ARAs closely and were introduced in 1983 (Chorzelski et al. 1984). These antibodies are detected by indirect immunofluorescence assay (IFA) on monkey oesophagus or human umbilical cord, but the technique is quite expensive and requires expertise in interpreting the results (Chorzelski et al. 1984, Ladinser et al. 1994). Further challenges associated with the test are the possibly reduced sensitivity in patients under two years of age or with mild villous atrophy (Abrams et al. 2004, Maglio et al. 2010). However, the specificity has been reported to be excellent – 95-100% – in most studies (Hill 2005a).

The identification of tTG in 1997 as an autoantigen of EmA revolutionized coeliac disease screening because it enabled the use of the easier ELISA test in diagnostics (Dieterich et al. 1997, Mäki 1997). The sensitivity of tTGab assays is generally higher, but specificity lower compared to EmA immunoassays, as differences in the quality of tTG antigen cause variations in the performance of commercial ELISA assays (Giersiepen et al. 2012). Not only serum, but also tTGab deposits have been found in the intestine and other organs (Korponay-Szabó et al.

2004). Furthermore, other types of transglutaminase (TG) have been found in extra-intestinal tissues, e.g. TG3 in skin in dermatitis herpetiformis and TG6 in blood vessels in brain in patients suffering from the neurological complications of coeliac disease (Caja et al. 2011). Other coeliac-related antibodies include deamidated gliadin peptides (Aleanzi et al. 2001), which have not yet found their place in clinical practice (Adriaanse and Leffler 2015).

Rapid point-of-care tests measuring tTG or deamidated gliadin peptide IgA type antibodies in a blood sample from the fingertip, making laboratory personnel or devices unnecessary, provide even easier screening of coeliac disease (Korponay-Szabó et al. 2005, Benkebil et al. 2013). However, the use of these tests is as yet unestablished. If the suspicion of coeliac disease is strong, and always if the test is positive, a laboratory evaluation of the coeliac disease serology should be conducted as further study.

There is an ongoing development of new diagnostic methods for coeliac disease such as gluten-specific T-cell detection by HLA-DQ-gluten tetramers (Sarna et al. 2017) and intestinal fatty acid-binding protein to directly measure the intestinal damage from coeliac disease (Adriaanse et al. 2017). These methods could be especially useful in patients already following a gluten-free diet and during follow-up, when evaluating the strictness and effects of the dietary treatment.

3.2 Small-bowel mucosal biopsy

Before advanced antibody tests, diagnosis of coeliac disease was dependent on typical symptoms and intestinal biopsies. Mucosal samples from the small intestine were first obtained by Watson suction capsule, and the upper gastrointestinal endoscopy was introduced in diagnostics in the 1980s. Due to the possible patchiness of the mucosal lesions in coeliac disease and problems with the quality of samples (Branski et al. 1996), it is recommended at least one biopsy be taken from the bulb and four from the distal parts of duodenum (Husby et al. 2012, Ludvigsson et al. 2014). However, caution should be exercised, especially in the interpretation of bulb biopsies, because several diseases other than coeliac disease can cause similar changes in this area (Taavela et al. 2016). Furthermore, biopsy samples should be correctly oriented and meticulously cut to enable a precise evaluation (Taavela et al. 2013b).

Currently, the most commonly used classification of small-bowel mucosal structure in coeliac disease is that introduced by Marsh in the 1990s (Marsh 1992).

He described the development of mucosal damage in coeliac disease from type 0 to type 3, the findings changing from a normal to an increased number of intraepithelial lymphocytes, to crypt hyperplasia and finally to villous shortening, indicating coeliac disease (Marsh 1992). Oberhuber modified this classification later by dividing type 3 changes into subgroups: 3a for mild villous atrophy, 3b for moderate villous atrophy and 3c for severe villous atrophy (Oberhuber et al. 1999).

The other more quantitative but also more time-consuming method of evaluating the structure of the small-bowel mucosa is by accurate variables measuring separately morphological changes (ratio of villous height and crypt depth, Vh/CrD) and inflammatory (intraepithelial lymphocyte density, IEL) changes (Kuitunen et al. 1982, Taavela et al. 2013b). A Vh/CrD ratio of <2.0 has usually been considered indicative of active coeliac disease (Kuitunen et al. 1982, Taavela et al. 2013b).

3.3 Problems with the diagnostics

Nowadays, coeliac disease patients are often found early by antibody screening: some have not yet developed villous atrophy at the time of evaluation. Patients with positive serology but without diagnostic findings in their small intestinal biopsy are classified as having "potential coeliac disease" (Ludvigsson et al. 2013). There is evidence that the mucosal damage progresses with a gluten-containing diet and that these patients may actually suffer from gluten-dependent symptoms and findings (Kurppa et al. 2009, Kurppa et al. 2010, Kurppa et al. 2014a). On the other hand, some studies have reported that only a minority of seropositive – and especially asymptomatic – patients without initial villous atrophy will develop atrophy on a gluten-containing diet, and that some of them even lose positive serology during follow-up (Auricchio et al. 2014, Volta et al. 2016, Mandile et al. 2018).

One risk of the serology-based approach is that patients with seronegative coeliac disease remain undiagnosed. These patients are typically elderly and have suffered various symptoms over decades (Salmi et al. 2006). They often have severe symptoms and small-bowel damage, and although coeliac disease antibodies cannot be detected from circulating blood, they are found in the intestine in the form of tTG-specific IgA deposits (Salmi et al. 2006, Salmi et al. 2010). In uncertain situations, another special diagnostic method is the evaluation of CD3+ and γδ+ T-cell receptor-bearing lymphocytes in mucosal samples (Salmi et al. 2010). Furthermore, the potential use of capsule endoscopy and double-balloon enteroscopy have been discussed, especially in the case of patients with a suspected

false-negative histology due to patchy atrophy or when small-bowel complications are suspected (Kurien et al. 2013, Tomba et al. 2016). However, especially in seronegative patients, it should be remembered that there are also other causes of villous atrophy, including giardiasis, tuberculosis and other infections, Crohn's disease, autoimmune enteropathy and some medications such as olmesartan (Aziz et al. 2017, Jansson-Knodell et al. 2018).

During recent years, an entity called non-coeliac gluten sensitivity has been studied increasingly. It is usually defined as gluten-responsive symptoms in the absence of coeliac disease and wheat allergy (Ludvigsson et al. 2013). Patients may suffer from various gastrointestinal or extra-intestinal symptoms that resolve on a gluten-free diet and return in a double-blinded gluten challenge (Fasano et al. 2015). However, at present, the pathogenesis, exact prevalence and prognosis of non-coeliac gluten sensitivity is obscure, nor is it known whether the symptoms are caused by gluten or by some other ingredient of wheat (Biesiekierski et al. 2013, Skodje et al. 2018). Some patients may present with increased gliadin antibodies, but currently there is no laboratory evaluation or biomarkers that can be used in precise diagnostics (Catassi et al. 2015).

4 TREATMENT FOR COELIAC DISEASE

4.1 Gluten-free diet

A strict, life-long gluten-free diet is currently the only accepted treatment for coeliac disease, and in most cases, it is curative (Husby et al. 2012, Ludvigsson et al. 2014). Based on current knowledge, the consumption of non-contaminated oats is safe in the great majority of coeliac disease patients (Janatuinen et al. 1995, Aaltonen et al. 2017, Pinto-Sánchez et al. 2017).

The stickiness and versatile properties of gluten makes it a popular ingredient in baking bread and pastries, and it is commonly also used in food preparation and the food industry (Case 2005). The daily gluten intake with a normal gluten-containing Western diet is approximately 15-20 grams (Tjon et al. 2010). A gluten amount of 30-100 mg per day is enough to cause abnormalities in the small-bowel mucosal structure of coeliac disease patients (Collin et al. 2004, Catassi et al. 2007), although gluten tolerance is individual and a single safety margin for gluten concentrations is difficult to set (Lähdeaho et al. 2011). The Food and Drug Administration and the European Commission have defined the term "gluten-free" as containing less than 20 milligrams of gluten per kilogram (Food and Drug Administration 2013; European Commission 2014).

A gluten-free diet is initiated after a verified diagnosis of coeliac disease. The diet results usually in the alleviation of gluten-dependent symptoms within few weeks, whereas normalization of the disease-specific antibodies and a complete healing of intestinal damage may take even several years, especially if the level of antibodies was significantly high and villous atrophy sufficiently severe at the time of diagnosis (Hansen et al. 2006, Webb et al. 2015). Because the skin symptoms of coeliac disease (dermatitis herpetiformis) usually respond slowly to dietary treatment, dapsone medication is often added in the beginning of the treatment to heal skin lesions (Collin et al. 2017).

If symptoms continue despite a strict gluten-free diet and if inadvertent dietary mistakes can be excluded, the explanation might be a coexisting disease (Barratt et al. 2011, Turco et al. 2011, Dewar et al. 2012). Also, refractory coeliac disease and small-bowel lymphoma should be ruled out (Dewar et al. 2012), although they are

both extremely rare, especially in patients diagnosed in childhood (Mubarak et al. 2011). Patients suffering from refractory coeliac disease do not respond to the dietary treatment (Ilus et al. 2014) and, for example, prednisolone, budesonide or a combination of prednisolone and azathioprine, biologic agents and immunosuppressants such as infliximab, cyclosporine and alemtuzumab have been tried as treatments (Rubio-Tapia and Murray 2010a). However, the treatment response and prognosis depend on the more specific type of the disease the patient is suffering from (Chapter 6.3).

4.2 Novel therapies

A gluten-free diet imposes a burden on many patients and can be difficult to follow (Hallert et al. 2002, Whitaker et al. 2009, Shah et al. 2014). Patients may also suffer from accidental exposure to gluten due to contaminated food, and some suffer from coeliac-related symptoms and continuing mucosal damage despite an apparently strict diet (Ilus et al. 2014, Laurikka et al. 2016). For these reasons, interest in developing new treatments for coeliac disease has grown significantly in recent years (Kurppa et al. 2014b).

Possible drugs for coeliac disease are targeted towards different steps of the process leading to the disease (Wungjiranirun et al. 2016). For example, genetically modified wheat variants (van den Broeck et al. 2009), detoxification of gluten (Gianfrani et al. 2007), gluten-binding agents (Pinier et al. 2009) and gluten-targeted endopeptidases (Mitea et al. 2008, Lähdeaho et al. 2014) have been studied, aimed at lessening gluten immunogenity and tight junction regulators (Leffler et al. 2012) altering intestinal permeability. Whether some of the biologics and immunomodulators could induce gluten tolerance has also been studied, along with drugs modifying, for example, the T-cell response to gluten (Goel et al. 2017). Chemokine receptor 9 (Olaussen et al. 2007), interleukin-15 (Korneychuk et al. 2014), tTG (Rauhavirta et al. 2013) and HLA-DQ2 (Xia et al. 2007), which play an important role in the innate and adaptive immunity to coeliac disease, have been targets of interest as well.

5 FOLLOW-UP ON COELIAC DISEASE

5.1 Current recommendations

Following up on coeliac disease is recommended to provide support in following a demanding life-long gluten-free diet, to improve health-related quality of life and to detect possible complications and co-morbidities as early as possible (Haines et al. 2008, Husby et al. 2012, Ludvigsson et al. 2014, Valitutti et al. 2017). Whether coeliac disease patients should be routinely screened for other autoimmune diseases has also been discussed (Canova et al. 2016).

Implementation of follow-up measures has varied greatly in different studies (Mozer-Glassberg et al. 2011, Herman et al. 2012, Torres et al. 2016), and even paediatric patients have been lost to follow-up as early as shortly after diagnosis (Mozer-Glassberg et al. 2011). Furthermore, in a 28-year follow-up study, only 22% of paediatric patients had taken part in any medical or dietary visits in adulthood (O'Leary et al. 2004). However, studies following paediatric patients to adulthood are small and scarce (Högberg et al. 2003, O'Leary et al. 2004). In addition, the actual significance of follow-up in long-term outcomes is obscure, although there is some evidence that unfollowed children may have a poor dietary compliance (Bardella et al. 1994, Jadresin et al. 2008, Barnea et al. 2014).

Some studies suggest that follow-up should be conducted annually face to face with a physician and/or dietician (Haines et al. 2008), and patients also seem to prefer this approach (Bebb et al. 2006, Haines et al. 2008). However, evidence and precise practical instructions about implementation of follow-up are as yet lacking. In adults, it is usually recommended that improvement of intestinal mucosa is be verified by a second small-bowel biopsy one year after the coeliac disease diagnosis (Wahab et al. 2002, Rubio-Tapia et al. 2010b, Sharkey et al. 2013). Nevertheless, the timing and need for this second biopsy has recently been questioned and a more personalized approach in follow-up proposed (Pekki et al. 2015, Pekki et al. 2017).

In children, the repeat biopsy is not believed to be necessary because the risk of developing malignancies is extremely rare, and the general anaesthesia necessary for a gastro-duodenoscopy always involves a risk of complications (Koletzko et al. 2017, Kara et al. 2018). Serology and clinical evaluations are used in following up on

paediatric patients (Husby et al. 2012), but whether these methods are sensitive enough and whether a repeated biopsy is necessary also in children is still under discussion (Koletzko et al. 2017, Leonard et al. 2017, Silvester et al. 2017). However, the limitation of both serology and mucosal samples is that small amounts or short exposures to gluten cannot always be detected (Silvester et al. 2017). In the future, measurement of gluten immunogenic peptides in urine and stool could be a possibility in order to amplify the evaluation of dietary strictness (Comino et al. 2016, Moreno et al. 2017).

5.2 Transition from paediatrics to adult care

In children with coeliac disease, parents are usually the ones who handle follow-up and dietary treatment in everyday life. In adolescence, responsibility for diet should be gradually transferred to the patients themselves, and thus this period of time is important in considering the success of treatment, also during adulthood. However, adolescence is also the most vulnerable period for dietary difficulties because of the many other changes in life and common need to be similar with peers (La Greca et al. 2002, Arnone and Fitzsimons 2012, Kurppa et al. 2012).

When coeliac disease is diagnosed in childhood, patients themselves may not later remember their symptoms from before diagnosis. Furthermore, even the most basic information about coeliac disease and reasons for its treatment may be poorly understood, if the age at diagnosis was young and/or only the parents were informed about these factors after diagnosis. These factors may reduce a patient's motivation to follow a gluten-free diet. On the other hand, the diet may be easier to follow if initiated and learned as part of everyday life at a young age (Högberg et al. 2003).

Current recommendations about the transition of coeliac disease patients from paediatrics to adult care are mostly based on professional opinion (Ludvigsson et al. 2016), and there are few studies reporting the implementation, success and associated factors of this transition (Kumar et al. 1988, Bardella et al. 1994, O'Leary et al. 2004). There are recommendations about the transition phase in gastrointestinal diseases in general and in other common chronic paediatric diseases such as type 1 diabetes and inflammatory bowel diseases (Crowley et al. 2011, Peters et al. 2011, Elli et al. 2015, Yerushalmy-Feler et al. 2017). Some of these practices may also be suitable for coeliac disease. Furthermore, ideas about the implementation of transition could be taken from other, although rarer, diet-controlled diseases such as phenylketonuria (Mütze et al. 2011, Gizewska et al. 2016).

6 CLINICAL PRESENTATION OF COELIAC DISEASE

The clinical features of coeliac disease have changed significantly over time concurrently with increasing knowledge about the disease. Nowadays, clinical manifestations are various, and patients range from asymptomatic found by screening to those with severe, even life-threatening complications (Ludvigsson et al. 2013).

6.1 Changing clinical picture

The first record of a coeliac disease-like condition was described in the second century by Greek physician Arataeus of Cappadocia, who labelled prolonged diarrhoea and fatty stools (steatorrhea), occasional stomach pain, weight loss and atrophy affecting adult patients "coeliac affection", or disorder of the gut (*koiliakos* in Greek; Adams 1856). The modern history of coeliac disease is often considered to have begun with Samuel Gee describing it as a chronic disease with abdominal distension and steatorrhea, without cystic fibrosis and affecting especially children (Gee 1888). However, the significance of gluten in the pathogenesis of coeliac disease was demonstrated significantly later (Anderson et al. 1952, Dicke and van de Kamer 1953).

At the end of the 1950s, per oral techniques of obtaining intestinal biopsies were developed (Sakula and Shiner 1957), which enabled a diagnosis of coeliac disease independently of clinical symptoms and resulting in an increased identification of new cases. Despite this, coeliac disease was still considered a rare disease affecting predominantly children under two years of age with prolonged diarrhoea and a failure to thrive – classical symptoms of malabsorption (Visakorpi 1974).

In the 1970s, coeliac disease seemed to disappear, until it was discovered that the age at diagnosis was simply rising and patients had milder symptoms than before (Mäki et al. 1988). The development of more practical and accurate coeliac disease antibody testing in the 1980s and 1990s revolutionized case-finding by enabling

screening for the disease at lower thresholds (Ladinser et al. 1994, Dieterich et al. 1997, Mäki 1997, Sulkanen et al. 1998).

In recent decades, an increasing prevalence and changing clinical presentation of coeliac disease has been reported from many developed countries (**Tables 1** and **2** and **Figure 1**). Gastrointestinal symptoms have been accompanied by extra-intestinal symptoms, and screening has also identified asymptomatic patients. The average age at diagnosis has risen from the previous under two to 5-9 years: in some studies even to 10-14 years (**Table 2**). Although most significant changes in the diagnostics of coeliac disease occurred before the twenty-first century, changes in clinical features and increasing incidence have been reported to continue in many countries (**Tables 1** and **2** and **Figure 1**).

6.2 Symptoms

Defining the symptoms of coeliac disease is no simple matter. Many apparently asymptomatic patients at diagnosis have discovered that earlier unrecognized complaints were later alleviated by a gluten-free diet (Ukkola et al. 2011, Rosén et al. 2014, Kinos et al. 2012). On the other hand, even when patients themselves recognize the symptoms, they may not seek medical help, or healthcare professionals may not suspect the symptoms are signs of coeliac disease (Ukkola et al. 2011, Kinos et al. 2012, Mahadev et al. 2016). Another important issue is the actual association between a symptom and coeliac disease. Common complaints are common also in coeliac disease patients, and the predictive value of many single symptoms of coeliac disease is poor (Katz et al. 2011, Rosén et al. 2014).

Gastrointestinal symptoms include so-called "classic" symptoms such as diarrhoea and vomiting and the more recently documented abdominal pain, constipation, bloating and discomfort (Steens et al. 2005, McGowan et al. 2009). The presence of intestinal complaints has varied significantly between different studies and time periods, although gastrointestinal symptoms are probably the best-recognized signs of coeliac disease (**Table 3**).

Extra-intestinal symptoms of coeliac disease include dermatitis herpetiformis, arthralgia and some neurological and psychological problems such as neuropathy, dementia and depression (**Table 3** and Bushara 2005, Ghozzi et al. 2014, Collin et al. 2017). Furthermore, most findings and complications of coeliac disease, such as anaemia, osteoporosis and enamel defects, could also be classified as extra-intestinal manifestations (Leffler et al. 2015). A wide variety of other symptoms, for example

Table 2. Studies evaluating changes in the clinical presentation of coeliac disease in children (published before 2016).

Reference	Country	Time periods [a]	Patients	Comparison of diagnostic characteristics between the first and last time period				
				Age, years	Villous atrophy	Classical picture	Atypical features	Screened [b]
Mäki et al. 1988	Finland	1961-1972 vs 1973-1984	96	<2 years: 78% vs 16%	ND	54% vs 18%[d]	Increased [k]	ND
Steens et al. 2005	Netherlands	1975-1990 [c] vs 1993-2000	1,240	Median: 1.5 vs 2.1	1993 vs 1999, partial: 10% vs 38%	Decreased [e]	Increased [l]	ND
Roma et al. 2009	Greece	1978-1987 vs 1998-2007	284	<2 years: 78% vs 29%	ND	99% vs 64%[f]	1% vs 36% [m]	0% vs 16%
Whyte et al. 2013	UK	1983-1989 [c] vs 2005-2011	249	Median: 4 vs 14	ND	88% vs 41% [g]	12% vs 23% [n]	0% vs 36%
Garampazzi et al. 2007	Italy	1987-1995 vs 1996-2006	307	Median: 4.2 vs 5.4	Subtotal: 70% vs 57%	Decreased [h]	Increased [o]	4% vs 9%
McGowan et al. 2009	North America	1990-1996 vs 2000-2006	235	Median: 2 vs 9	Total: 64% vs 44%	67% vs 19% [i]	33% vs 53% [p]	0% vs 28%
Gocke et al. 2015	Turkey	2005-2008 vs 2008-2012	191	Mean: 6.9 vs 9.3	Subtotal or total: 76% vs 79%	53% vs 35% [j]	42% vs 47% [q]	5% vs 16%

[a] Only the first and last reported time period included.
[b] Risk-group screening.
[c] Published earlier.
ND: no data.
Classical picture: [d] diarrhoea together with poor growth; [e] diarrhoea, abdominal distention and growth failure; [f] abdominal distention, diarrhoea, failure to thrive, weight loss, anorexia or irritability; [g] diarrhoea, steatorrhea, iron deficiency anaemia, weight loss or growth failure; [h] failure to thrive, abdominal distension or chronic diarrhoea; [i] weight loss or diarrhoea with failure to thrive; [j] not defined.
Atypical features: [k] asymptomatic or monosymptomatic patients, who had for example arthritis or arthralgia, delayed puberty or minimal abdominal symptoms; [l] abdominal pain; [m] constipation, abdominal pain, vomiting, short stature and anaemia; [n] no manifestations of malabsorption; [o] constipation, recurrent abdominal pain, impaired height development, isolated anaemia, asymptomatic patients with coeliac disease in the family, other; [p] any gastrointestinal symptom without weight loss or failure to thrive or extra-intestinal symptom or short stature or anaemia; [q] not defined.

headache and tiredness, have also been proposed to be associated with coeliac disease, but their true association and response to a gluten-free diet remain obscure (Jericho et al. 2017). The pathogenesis behind extra-intestinal manifestations is relatively poorly known. Chronic inflammation, malabsorption and nutritional deficiencies might be involved, as well as adaptive immunity, including coeliac autoantibodies TG2, TG3 and TG6 and their possible organ-specific roles (Korponay-Szabó et al. 2004, Leffler et al. 2015).

Table 3. Prevalence of different symptoms and findings in children diagnosed with coeliac disease before and from the year 2000.

	Prevalence in different studies (%)	
	Before 2000	**From 2000 on**
Gastrointestinal symptoms		
Diarrhoea	52-78	12-49
Vomiting	18-39	3-17
Abdominal pain	6-90	14-77
Constipation	0-30	5-41
Extra-intestinal symptoms/findings		
Poor growth/failure to thrive	24-89	11-48
Enamel defects	15-83 [a]	1-6
Decreased bone mineral density	50-58	30
Anaemia	3-28	7-74
Neurological/psychiatric symptoms [b]	37-51	0-24
Elevated liver enzymes	32	9-40
Oral aphtous ulcers	16	0-16
Delayed puberty	6	ND
Arthralgia/arthritis	5	0-11
Dermatological symptoms	ND	0-15

Data collected from following studies: Aine et al. 1990, Ben Hariz et al. 2007, Di Biase et al. 2009, Farre et al. 2002, Garampazzi et al. 2007, Gokce and Arslantas 2015, Jericho et al. 2017, Kalayci et al. 2001, Mubarak et al. 2013, Mäki et al. 1988, Nurminen et al. 2018, Rashid et al. 2005, Roma et al. 2009, Savilahti et al. 2010, Steens et al. 2005, Tau et al. 2006, White et al. 2013b, Zelnik et al. 2004.

[a] Evaluated in adult patients.
[b] For example headache, developmental disorders, hypotonia, epilepsy, depression, mood swings and ataxia.
ND: no data.

6.3 Clinical findings and complications

A clinical finding can be defined as an abnormality revealed in a clinical examination or laboratory result. Patients themselves cannot experience findings, and these are often more objective and measurable than symptoms. Complications of coeliac disease often result from a longer period of time with ongoing disease. Complications may become permanent if treatment is not initiated early enough.

The malabsorption and chronic inflammation associated with coeliac disease can result in anaemia and other laboratory abnormalities, such as vitamin deficiencies (Schøsler et al. 2016, Rajalahti et al. 2017). Coeliac disease-associated anaemia is usually caused by iron deficiency, but patients may also suffer from vitamin B12 and folate deficiencies (Harper et al. 2007). Although anaemia can present as a sole finding of coeliac disease, it is often part of a severe form of the disease (Abu Daya et al. 2013, Rajalahti et al. 2017).

Elevated liver enzymes are frequently seen in untreated coeliac disease patients (**Table 3**). The values are usually only mildly elevated and resolve well after the initiation of a gluten-free diet (Korpimäki et al. 2011, Äärelä et al. 2016), but coeliac disease patients may also suffer from severe liver disease (Kaukinen et al. 2002). Whether liver enzymes should be routinely screened in all coeliac disease patients remains to be studied.

6.3.1 In children

Impaired growth in coeliac disease has classically been associated with severe malabsorption syndrome (Visakorpi and Mäki 1994). However, it is currently also recognized as a sole sign of coeliac disease (Nurminen et al. 2015, Saari et al. 2015). Otherwise asymptomatic patients with growth disturbances have been diagnosed at an older age than those suffering from malabsorption (Nurminen et al. 2015), and although the specific pathogenesis is as yet obscure, increased levels of anti-pituitary antibodies and decreased levels of insulin-like growth factor-I, for example, in addition to malabsorption, have been correlated with changes in growth (Jansson et al. 2001, Delvecchio et al. 2010).

Abnormal puberty in coeliac disease is believed to result from hormonal imbalances and hypogonadism. Later in life, if coeliac disease remains untreated, women may suffer also infertility and early menopause (Bona et al. 2002).

A delayed diagnosis of coeliac disease may result in impaired bone mineral density (Kalayci et al. 2001), or even osteomalacia and rickets, which are rare today in developed countries. Abnormal bone structure is likely explained by multiple factors such as hypocalcaemia and vitamin D deficiency caused by malabsorption, secondary hypoparathyroidism, and proinflammatory cytokines released due to chronic intestinal inflammation. Furthermore, the possible role of osteoprotegerin autoantibodies has been discussed (Riches et al. 2009, Vaziri-Sani et al. 2017). The risk of decreased bone mineral density increases if a patient reduces his or her use of dairy products, suffers from other autoimmune diseases, has a low body mass index or does not maintain a strictly gluten-free diet (Krupa-Kozak 2014).

Aphthous stomatitis and enamel defects are the most common, although unspecific, oral manifestations of coeliac disease. The latter are permanent if formed in early childhood (Cheng et al. 2010), whereas aphthous ulcers usually respond well to a gluten-free diet (Pastore et al. 2008).

6.3.2 In adults

Apart from enamel defects, decreased bone accrual and short stature, most permanent complications associated with untreated coeliac disease do not manifest themselves until adulthood (**Figure 2**). Infertility and fractures are often encountered in early adulthood, whereas liver failure and neurological complications such as neuropathy, gluten ataxia and dementia typically present in older patients who have likely suffered untreated disease for decades. To prevent these complications, it would be logical to conclude that coeliac disease should be diagnosed and treated as early as possible, although scientific evidence supporting this theory is lacking (**Figure 2**).

Non-responsive coeliac disease is a rare condition affecting 0.3-2% of patients who are usually over 50 years old (Ilus et al. 2014, Malamut and Cellier 2015). The most common reason for continuing symptoms, elevated antibody levels and mucosal damage is the inadvertent use of gluten. If dietary non-adherence and other possible diseases causing small-bowel villous atrophy are excluded (Chapter 3.3), and the symptoms and atrophy persist or recur over 6-12 months, the patient is defined as suffering from refractory coeliac disease (Rubio-Tapia and Murray 2010a, Malamut and Cellier 2015), although this time interval could be considered to be too short for the mucosal structure to heal (Pekki et al. 2017).

Refractory coeliac disease is grouped into two types which differ in prognosis. Type 1 resembles non-treated, active coeliac disease, whereas type 2 is characterized by the presence of atypical intraepithelial lymphocytes, indicating a low-grade intraepithelial lymphoma and subsequent risk of enteropathy-associated T-cell lymphoma and ulcerative jejunitis (Rubio-Tapia and Murray 2010, Malamut and Cellier 2015). In refractory coeliac disease type 2, the five-year mortality is approximately 50% (Rubio-Tapia and Murray 2010). In paediatric coeliac disease patients, the risk of non-responsive coeliac disease and consequent complications is practically non-existent (Mubarak et al. 2011).

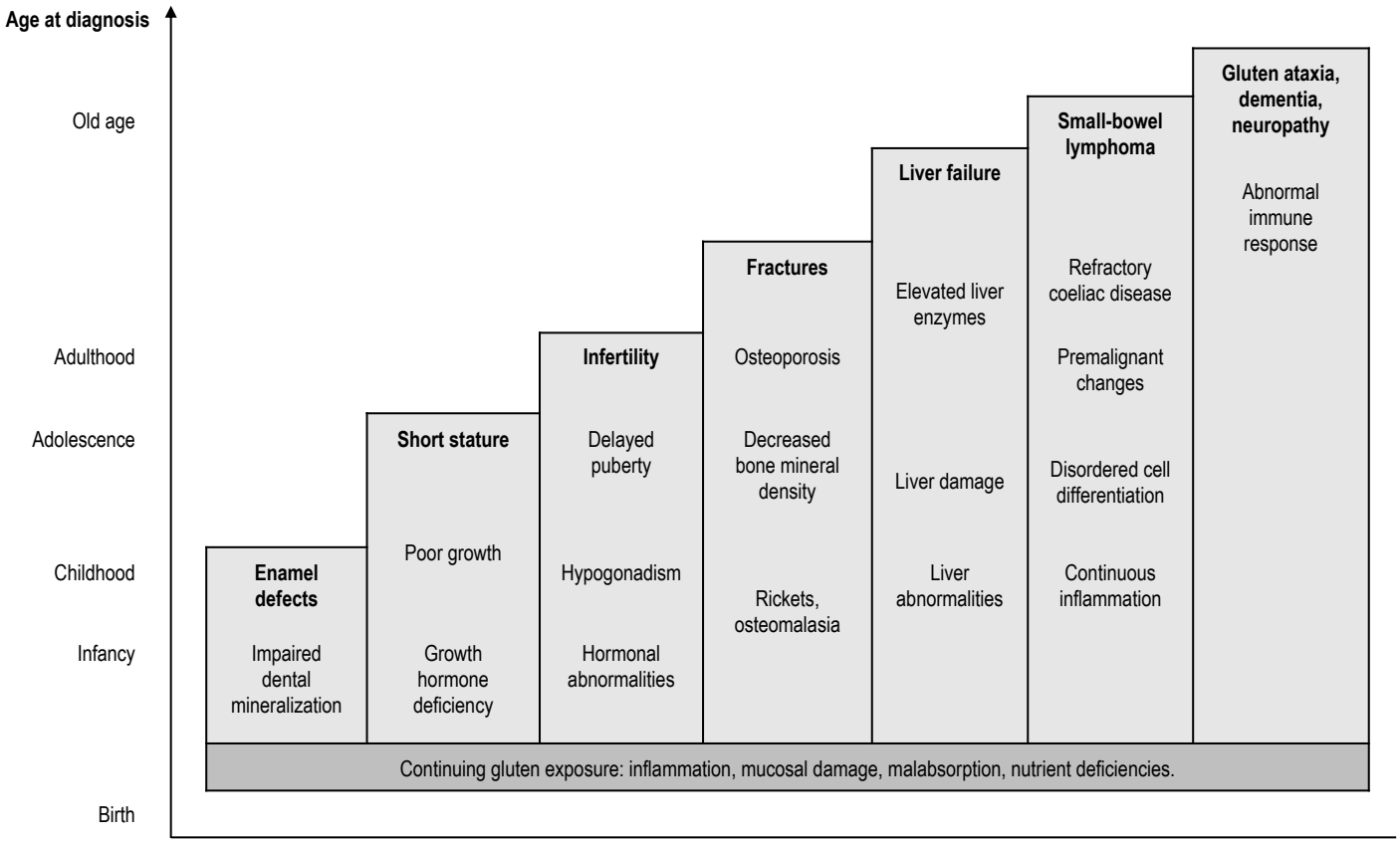

Figure 2. Complications associated with untreated coeliac disease, and typical age at presentation, possible mechanisms and development.

7 SCREENING FOR COELIAC DISEASE

Screening has traditionally been defined as identification of an unrecognized condition by a test which tentatively sorts out those with and without the disease (Wilson and Jungner 1968). Screening can be focused on an entire population (mass screening) or on selected high-risk groups (Wilson and Jungner 1968). The simplest diagnostic approaches, also in coeliac disease, can be categorized as case-finding, risk-group screening and mass screening. To find all coeliac disease patients, screening should be focused on the entire population or at least gluten-using genetically predisposed individuals (**Figure 3**).

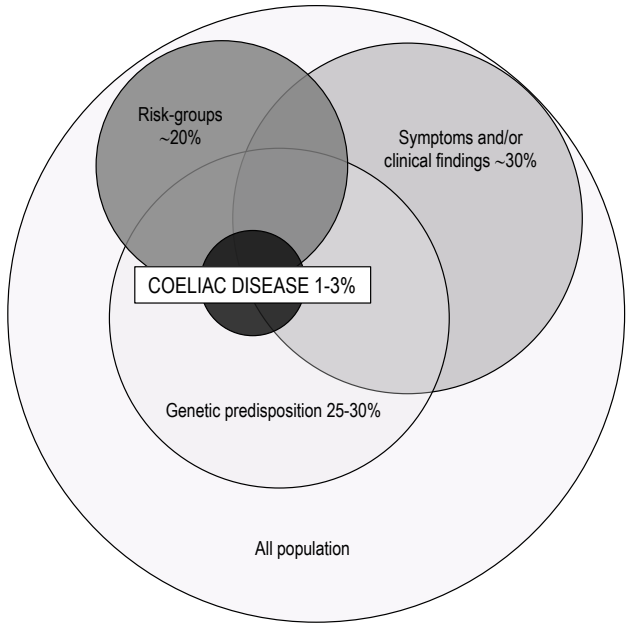

Figure 3. The prevalence of coeliac disease in the unselected population. In theory, diagnostic evaluations could be focused on those with a genetic risk of developing the disease. The disease risk is also markedly increased among subjects suffering from other autoimmune diseases and those with coeliac disease in the family (risk groups) and those with coeliac disease-associated symptoms or clinical signs, but not all these individuals have a genetic predisposition and therefore be at risk of developing coeliac disease. Percentages were estimated based on data from Sollid et al. 1989, Polvi et al. 1996, Sategna Guidetti et al. 2001, Mäki et al. 2003, Viljamaa et al. 2005b, Myléus et al. 2009, and Rosen et al. 2011.

Table 4. The feasibility of the World Health Organization's screening criteria for coeliac disease.

Screening criteria	Coeliac disease
The condition is an important health problem.	It affects 1-3% of population.
Clinical case-finding is difficult.	Most patients are unrecognized.
A screening test is available and accurate.	The sensitivity and specificity of modern serological tests is high.
There is an accepted treatment.	A gluten-free diet alleviates symptoms and mucosal damage and prevents future complications, especially if initiated in childhood.
The natural history of the condition is understood.	Whether also asymptomatic patients are at risk of developing complications and whether potential coeliac disease always develops into a clinical disease are unclear.
The definition for who should be treated as patients is clear.	Asymptomatic and potential coeliac disease patients have been scarcely studied, and whether they should always be treated is not known.
Overall benefits should overcome harms.	Whether the benefits of a gluten-free diet exceed its possible burden in asymptomatic patients is not known.
The cost-effectiveness is economically balanced.	There is a lack of evidence.

Modified from Wilson and Jungner 1968, Andermann et al. 2008 and Ludvigsson et al. 2015.

The World Health Organization's criteria for screening for disease from 1968 and their update in 2008 have been considered golden rules when evaluating whether a condition is appropriate for screening (Wilson and Jungner 1968, Andermann et al. 2008). Currently open issues concerning screening for coeliac disease are the benefits of screening for asymptomatic patients, difficulties with the diagnostics of potential or early disease, and the cost-effectiveness of screening (**Table 4**).

7.1 Different diagnostic strategies

Currently, the diagnostics of coeliac disease rely significantly on clinical case-finding in many countries (McGowan et al 2009, White et al. 2013a, Gokce and Arslantas 2015). The effectiveness of this approach is highly affected by the level of knowledge

of healthcare professionals and patients. The best-case scenario is that coeliac disease is suspected whenever a patient suffers from symptoms or there are findings that could indicate the disease. On the other hand, even "typical" coeliac disease symptoms have poor predictive value for the actual disease (Katz et al. 2011, Rosén et al. 2014), and only those who attend routine medical examinations or seek medical help because of their complaints can be found. The possibility of evaluation and awareness of the disease often depends on the socio-economic and educational background of patients and their families (Barbero et al. 2014, Whyte et al. 2014, Zingone et al. 2015), and therefore case-finding may cause inequality.

Another approach is to screen selected high-risk groups (Chapter 2.2). Although the definition of "risk group" has varied in different recommendations, most of them have included in the risk groups the first-degree relatives of coeliac disease patients and those with type 1 diabetes (**Table 5**). However, whether other risk groups such as patients with Down's syndrome or autoimmune thyroidal diseases should be included in routine screening programs is unclear. Currently, screening of family members of coeliac disease patients and of children with type 1 diabetes is carried out in many centres (Pham-Short et al. 2015).

Repeated mass screening of the entire population could be considered the only way to find the great majority of coeliac disease patients, but since coeliac disease can develop at any age (Vilppula et al. 2009), the optimal age and frequency of screening is not known. Based on findings from a recent prospective multicentre birth cohort study, the Environmental Determinants of Diabetes in the Young, the most likely age at which the development of autoantibodies occurred was before the age of three in children with a genetic risk of coeliac disease (Hagopian et al. 2017). Whether this could be generalized to all populations is unclear. Among others, Catassi and Fasano (2014) have proposed mass screening by determining HLA genotype at birth and then focusing later screening with coeliac antibodies on those 20-30% with the correct genetic background (Catassi and Fasano 2014). However, these same patients could mostly also be found by targeted risk-group screening, because those with type 1 diabetes or coeliac disease in the family often share these HLA risk alleles (Binder et al. 2017, **Figure 3**).

The cost-effectiveness of different diagnostic approaches, including screening for coeliac disease, have scarcely been studied, and currently the evidence is insufficient to reach a conclusion about the best approach (Shamir et al. 2006, Green et al. 2008, Hershcovici et al. 2010).

Table 5. Recommendations for coeliac disease screening in children and adults.

Reference	Organization	Target population	Recommendation about screening
Bibbbins-Domingo et al. 2017	USPSTF	≥3 years old, children and adults	Risk-groups: not stated. Population: not stated.
Downey et al. 2015	NICE	Children and adults	Risk-groups (T1D, AIT, family members): yes. Population: not stated.
Ludvigsson et al. 2014	British Society of Gastroenterology	Adults	Risk-groups (T1D, family members, Down syndrome, IBS): yes. Population: no.
Murch et al. 2013	BSPGHAN and Coeliac UK	Children	Risk-groups (T1D, AIT, family members, Down, Turner and Williams syndromes, IgA deficiency and ALD): yes. Population: no.
Rubio-Tapia et al. 2013	ACG	Children and adults	Risk-groups (symptomatic T1D, family members): yes. Population: no.
Husby et al. 2012	ESPGHAN	Children	Risk-groups (T1D, AIT, family members, Down, Turner and Williams syndromes, IgA deficiency and ALD): yes. Population: not stated.
Hill et al. 2005b	NASPGHAN	Children	Risk-groups (T1D, AIT, family members, Down, Turner and Williams syndromes, IgA deficiency and ALD): yes. Population: not stated.
NIH et al. 2004	NIH	Children and adults	Risk-groups: no. Population: no.

ACG: American College of Gastroenterology; AIT: autoimmune thyroidal disease; ALD: autoimmune liver disease; BSPGHAN: British Society for Paediatric Gastroenterology, Hepatology and Nutrition; ESPGHAN: European Society for Paediatric Gastroenterology, Hepatology and Nutrition; IBS: irritable bowel syndrome (in adults); NASPGHAN: North American Society for Pediatric Gastroenterology, Hepatology and Nutrition; NICE: National Institute for Health and Care Excellence; NIH: National Institutes of Health; T1D: type 1 diabetes; USPSTF: US Preventive Services Task Force.

7.2 Risks associated with untreated coeliac disease

The natural course of untreated coeliac disease is as yet partly unknown. Studies conducted in asymptomatic screen-detected patients are scarce, and whether their risk of developing coeliac disease-associated complications is comparable to that of symptomatic patients has been questioned (Ludvigsson et al. 2015, Chou et al. 2017).

The severity of mucosal damage at diagnosis might be used to describe the risk of developing complications, but findings on the association between clinical presentation and the degree of villous atrophy have been inconsistent (Brar et al. 2007, Thomas et al. 2009, Dorn et al. 2010, Taavela et al. 2013a). Nevertheless, also screen-detected patients suffer from complications such as underachievement, growth disturbances and decreased bone mineral density, and many of them experience unrecognized symptoms (**Table 6** and Verkasalo et al. 2005). Thus "asymptomatic" is not a synonym for "screen-detected". However, whether they are at risk of developing permanent complications such as fractures, infertility, refractory coeliac disease and small-bowel lymphoma (Chapter 6.3) is not known.

Unrecognized complaints may impair quality of life and increase the risk of continuing symptoms, even on a gluten-free diet, the risk being higher in those with a longer duration of symptoms before the diagnosis (Paarlahti et al. 2013). Symptoms that continue during treatment are also associated with a reduced quality of life (Gray and Papanicolas 2010, Barratt et al. 2011, Paarlahti et al. 2013).

Several studies have evaluated mortality in both treated and untreated coeliac disease patients, but the results have been contradictory (Lohi et al. 2009, Ludvigsson et al. 2009, Rubio-Tapia et al. 2009, Choung et al. 2017). However, this could be explained by differences in the evaluated patient populations (Biagi and Corazza 2015). Mortality rates could be affected by the severity of coeliac disease at diagnosis, which can depend on the diagnostic delay and clinical presentation: for example, patients with dermatitis herpetiformis seem to have decreased mortality rates compared with the general population (Viljamaa et al. 2006). Furthermore, whether patients adhere to an early-initiated strict gluten-free diet or remain unrecognized and untreated probably also affects their prognosis. Current evidence is insufficient to justify screening based on a possibly increased mortality in undetected coeliac disease patients.

Table 6. Characteristics of screen-detected children with coeliac disease at the time of diagnosis.

Reference	Country	Patients	Symptoms	Growth	Other
Mass-screened					
Al-Hussaini et al. 2017	Saudi Arabia	Screen-detected: 103 Non-coeliac controls: 7,827	64%	Poor growth more common than in controls: 17% vs 8%.	ND
Jansen et al. 2017	Netherlands	Screen-detected: 31 Potential coeliac disease: 10 Non-coeliac controls: 10	68%	BMI lower compared to potential coeliac disease and controls.	ND
van der Pals et al. 2014	Sweden	Screen-detected: 239 Non-coeliac controls: 12,227	ND	Lower weight, height and BMI than in controls. 4% underweight, 82% normal weight and 14% overweight.	ND
Nordyke et al. 2011	Sweden	Screen-detected: 153 Clinically detected: 66 Non-coeliac controls: 6,844	ND	ND	Health-related quality of life was similar in the different groups.
van Koppen et al. 2009	Netherlands	Screen-detected: 32 Non-coeliac controls: 8,159	41%	Poor growth: 3%.	General health was worse in all screened patients and quality of life was lower in symptomatic screened patients than in controls.
Korponay-Szabó et al. 2007	Hungary	Screen-detected: 32 Non-coeliac controls: 2,566	ND	31% underweight. Poor growth more common than in controls.	Anaemia in 22%. General health and bodily pain scores were worse than in controls.
Risk-group screened					
Björck et al. 2017	Sweden	Genetic risk + coeliac disease: 71 Matched non-coeliac controls: 142	ND	No difference in BMI, lean mass or fat mass.	Lower BMD in total body and spine, lower vitamin D3 levels, higher PTH levels.

Laitinen et al. 2017	Finland	T1D + coeliac disease: 22 Clinically detected: 498	55%	Poor growth more common than in clinically found: 14% vs 41%.	Anaemia (20%), EmA titres and degree of villous atrophy were comparable to clinically found.
Agardh et al. 2015	Sweden, Germany, Finland, USA	Genetic risk + coeliac disease: 340 Coeliac autoimmunity [a]: 914 tTGab negative controls: 5,792	27-34%	Comparable to coeliac autoimmunity patients and controls.	Symptoms were more common in 2-3 year-old, but not in 4-year-old coeliac autoimmunity patients compared with controls.
Tsouka et al. 2015	Canada	T1D + coeliac disease: 41 Clinically detected only: 41	48%	Better height, weight and BMI than in CD only.	ND
Saadah et al. 2012	Saudi Arabia	T1D + coeliac disease: 48 T1D only: 382	12%	Lower height and weight than in T1D only.	More anaemia and lower albumin levels. No difference in HbA1c levels.
Taler et al. 2012	Israel	T1D + coeliac disease: 68 T1D only: 131	26%	Comparable to patients with T1D only.	No difference in glycaemic control, diabetic ketoacidosis or severe hypoglycaemia.
Kinos et al. 2012	Finland	Family risk / T1D / AIT / trisomy 21 + coeliac disease: 43 Symptom-detected: 88	65%	ND	Overall health was similar between the groups.
Fröhlich-Reiterer et al. 2011	Austria and Germany	T1D + coeliac disease: 411 T1D only: 17,661	ND	Lower height and weight than in T1D only.	No difference in metabolic control or diabetes complications.
Turner et al. 2009	Canada	Family risk + coeliac disease, asymptomatic: 14 Symptomatic: 60	ND	ND	Bone mineral density was similar in the different groups. tTGab values were lower in asymptomatic patients.
Hansen et al. 2006	Denmark	T1D + coeliac disease: 33 T1D only: 236	85%	Lower height and weight than in T1D only.	Age at T1D diagnosis was lower in coeliac disease patients than in those with T1D only.

AIT: autoimmune thyroidal disease; BMD: bone mineral density; BMI: body mass index; EmA: endomysial antibody; HbA1c: glycated blood haemoglobin; ND: no data; PTH: para-thyroid hormone; tTGab: tissue transglutaminase antibodies; T1D: type 1 diabetes.

[a] Defined as positive tTGab in two successive samples.

7.3 Gluten-free diet in screen-detected patients

Initiation of a gluten-free diet usually results in an alleviation of symptoms and findings of coeliac disease and improved quality of life (**Table 7**). Furthermore, most disease-associated complications (**Figure 2**, page 45) can be prevented by early-initiated dietary treatment. However, a life-long gluten-free diet may also affect patients' lifestyle – e.g. eating in restaurants, traveling and other social activities – if the availability of gluten-free products is poor (Rashid et al. 2005, Sverker et al. 2005, Altobelli et al. 2013, MacCulloch and Rashid 2014). Also, the products are often more expensive than their gluten-containing counterparts (Lee et al. 2007, Panagiotou and Kontogianni 2017).

Patients have reported anger, embarrassment and fear of being a burden because of the diet (Rashid et al. 2005, Sverker et al. 2005, Tapsas et al. 2014). Also, unwanted attention due to special diet and even feelings of being stigmatized because of a chronic illness have been described (Rashid et al. 2005, Sverker et al. 2005, Tapsas et al. 2014). Furthermore, significant changes in daily diet may increase the risk for overweight, an unfavourable lipid profile, an unbalanced diet and nutritional deficiencies (Bardella et al. 2000, Hopman et al. 2006, Norsa et al. 2013, Diamanti et al. 2014).

The diagnosis of coeliac disease and adherence to a strict gluten-free diet may cause anxiety and diminish quality of life, especially in screen-detected patients who considered themselves healthy before screening. In most studies, the quality of life of screened patients was comparable to that of healthy controls, the general population or clinically detected patients on a gluten-free diet (**Table 7**). However, the follow-up time in these studies was at most ten years, which is insufficient to evaluate possible long-term effects and difficulties with the diet after the transition from childhood to adulthood. To justify screening for coeliac disease, positive effects of the treatment should outweigh possible negative aspects. This is logical and has been demonstrated in symptomatic patients, but due to the relatively scarce evidence about screen-detected and especially asymptomatic patients, screening recommendations have remained inconsistent (**Table 5**, page 49).

Adherence to a gluten-free diet in all patients diagnosed with coeliac disease in childhood varies from 23% to 100% and in screen-detected patients between 23% and 89% (**Table 8**). The association between diagnostic approach and dietary adherence differs from study to study, but it should be noted that, in most of these

studies, the average follow-up time was under ten years as well. The few studies systematically evaluating patients diagnosed in childhood and followed up on until adulthood report adherence to the diet to be 36-80%, but whether these studies included screen-detected patients is not reported. Also, other studies included patients diagnosed in childhood, but they were evaluated only as part of the entire adult study population (**Table 8**). The clinical presentation in screen-detected patients is often milder, and some of them are asymptomatic, which has been proposed to affect their dietary adherence. Nevertheless, long-term evidence about dietary adherence in the patient group diagnosed in childhood is lacking.

Table 7. Studies evaluating follow-up outcomes in children diagnosed with coeliac disease by screening.

Reference	Country	Patients	Follow-up time	Effects of gluten-free diet and quality of life in screened patients
Mass screening				
Webb et al. 2015	Sweden	Screen-detected: 201	1 year	tTGab normalized in 85%, and most of those with highest levels at diagnosis had halved their tTGab.
Nordyke et al. 2013	Sweden	Screen-detected: 103 Non-coeliac controls: 483	1 year	Health-related quality of life was comparable to that of controls.
van Koppen et al. 2009	Netherlands	Screen-detected: 32 Non-coeliac controls: 8,159	1 and 10 years	1 y: symptoms alleviated, and EmA, tTGab and intestinal mucosa normalized in all. Quality of life was better or remained unaffected. 10 y: improved health status in 66%. Quality of life was comparable to that of controls. 19% children remained asymptomatic on gluten-containing diet.
Korponay-Szabó et al. 2007	Hungary	Screen-detected: 32	6 months	Hb, BMI and general health improved, and EmA, tTGab and bodily pain decreased.
Tommasini et al. 2004	Italy	Screen-detected: 30	8 months, 1, 1.5 and 2 years	Symptoms resolved in all, and EmA and tTGab decreased. Overall effect of the diet was considered positive in 38%, negative in 6% and non-existent in 56% by parents of the patients.
Fabiani et al. 2000	Italy	Screen-detected: 22 Symptom-detected: 22	5 years	Groups did not differ in depression or anxiety scores.
Risk-group screening				
Laitinen et al. 2017	Finland	T1D + coeliac disease: 22 Clinically detected: 498	Median 13 months	Positive clinical and serological response in 95%.

Sud et al. 2012	Canada	T1D + coeliac disease: 28 T1D only: 40	0.5 years or longer	Coeliac disease diagnosis was not associated with quality of life, but social functioning scores were lower in coeliac disease patients than in those with T1D only.
Kinos et al. 2012	Finland	Family risk / T1D / AIT / trisomy 21 + coeliac disease: 43 Symptom-detected: 88	1 year	Symptoms alleviated: 78% vs 86% (also in 50% of asymptomatic patients). Improvement in daily life: 73% vs 69%. Satisfied with diagnosis: 93% vs 88%. Also, health concerns were reduced, and overall health improved similarly in both groups.
Hansen et al. 2006	Denmark	T1D + coeliac disease: 33	2 years	Antibodies normalized in 77%, symptoms alleviated, and weight increased significantly. Hb, MCV and serum ferritin increased, but HbA1c did not change. In follow-up intestinal biopsy, mucosa was normal in 78% and partially recovered in 22%.

AIT: autoimmune thyroidal disease; BMI: body mass index; EmA: endomysial antibody; Hb: haemoglobin; HbA1c: glycated haemoglobin; MCV: mean corpuscular volume; ND: no data; tTGab: tissue transglutaminase antibody; T1D: type 1 diabetes.

Table 8. Adherence to a gluten-free diet and its association with clinical presentation at least one year after a coeliac disease diagnosis in patients diagnosed in childhood. Studies published before the year 2000 excluded.

Reference	Country	Number of children	Screened patients included	Time from diagnosis	Adherence to a gluten-free diet and its association with clinical presentation
Children					
Kinos et al. 2012	Finland	131	Yes	1 year	Screened 71%, symptom-detected 84%
Kurppa et al. 2012	Finland	94	Yes	Median 7 years	All patients 81%, not associated
Roma et al. 2010	Greece	73	Yes	Mean 4 (range 1-16) years	All patients 58%, screened 89%
Torres et al. 2016	Spain	480	Yes	Mean 8 years	All patients 97% [a]
Charalampopoulous et al. 2013	Greece	90	Yes	Median 4 (range 2-7) years	All patients 44% [a]
Sud et al. 2012	Canada	28	Yes	0.5 years or longer	All patients 79% [a]
Bellini et al. 2011	Italy	156	Yes	Mean 4 years	All patients 78% [a]
Tommassini et al. 2004	Italy	30	Yes	9, 12, 18 and 24 months	All patients 100% [a]
Taghdir et al. 2016	Iran	65	ND	Range 1-144 months	All patients 54% [a]
MacCulloch et al. 2014	Canada	126	ND	Median 3 (range 0.5-15) years	All patients 70% [a]
Jadresin et al. 2008	Croatia	71	ND	Mean 9 years	All patients 59% [a]
Patwari et al. 2003	India	65	ND	Mean 22 (range 6-48) months	All patients 89% [a]
Adolescents					
Fabiani et al. 2000	Italy	44	Yes	≥5 years	Screened 23%, clinically found 68%
Webb et al. 2015	Sweden	193	Yes	1 year	All patients 82% [a]

Altobelli et al. 2013	Italy	140	Yes	Range 0-18 years	All patients 87% [a]
Tapsas et al. 2014	Sweden	316	ND	Mean 7 years	All patients 97% [a]
Wagner et al. 2008	Austria and Germany	281	ND	Median 8-11 years	All patients 80% [a]
Hopman et al. 2006	Netherlands	132	ND	Mean 10 years	All patients 75% [a]
Currently adults diagnosed in childhood					
O'Leary et al. 2004	Ireland	50	ND	Mean 29 (range 22-45) years	All patients 50% [a]
Högberg et al. 2003	Sweden	29	ND	Range 17-24 years	Age at dg: ≤4 years, 80%; >4 years, 36% [a]
Adults [b]					
Mahadev et al. 2016	United States	211 [c]	Yes	Median 4 (range 0-36) years	Screened 93%, symptom-detected 95%
Paavola et al. 2012	Finland	466 [c]	Yes	Median 7-9 (range 1-53) years	Screened 88%, symptom-detected 88%
Lee et al. 2012	United States	227	ND	From 0 to >16 years	All patients 98% [a]
Hopman et al. 2009	Netherlands	53	ND	Range 12-52 years	All patients 62% [a]
Green et al. 2001	United States	97 [d]	ND	On average 8 years	All patients 68% [a]

[a] Dietary adherence in the entire study group; association with clinical presentation was not studied.
[b] Some patients diagnosed in childhood, but not evaluated separately.
[c] Number of patients diagnosed in childhood not reported.
[d] 62% did not remain on a gluten-free diet after childhood and were re-diagnosed in adulthood.
Dg: diagnosis; ND: no data.

THE PRESENT STUDY

8 AIMS

The main aims of the present study were to evaluate changes in the clinical picture of coeliac disease in children in recent decades and to clarify diagnostic characteristics and long-term outcomes extending to adulthood in patients found by screening in groups at risk of the disease.

The specific aims were:

1. To characterize changes in clinical and histological presentations of Finnish children diagnosed with coeliac disease from the 1960s to the present (**I**), and to evaluate secular trends in the clinical incidence of coeliac disease autoimmunity in children in the twenty-first century (**I**).

2. To compare clinical and histological characteristics in clinically found and screen-detected children with coeliac disease at the time of diagnosis (**II, III**).

3. To compare patients detected by risk-group screening to those found due to clinical suspicion after short-term follow-up regarding adherence and treatment response to a gluten-free diet (**II**) and after transition to adulthood regarding dietary adherence, quality of life and overall health (**III**).

9 PATIENTS

9.1 Patients in Study I

The study cohort comprised 596 children who had confirmed coeliac disease and were diagnosed before they reached the age of 18. Data were collected from the paediatric coeliac disease research database, which included patients diagnosed with coeliac disease in 1966-2013. Diagnoses before the 1970s were made mostly by the paediatric department of Helsinki University Hospital and diagnoses after that by the Tampere University Hospital. Most coeliac disease diagnoses were made by or under the supervision of the Study I authors. Data were abstracted from medical records and in some cases supplemented with personal interviews. Furthermore, a significant proportion of patients had participated in a prospective study enrolment.

Additionally, 687 children who were referred to the paediatric gastroenterology clinic of Tampere University Hospital due to suspected coeliac disease in 2001-2013 were included in the calculations of annual clinical incidences of coeliac disease autoimmunity. Inclusion criteria for these patients were age under 16 years and positive EmA and/or tTGab results, regardless of the small-bowel biopsy results.

9.2 Patients in Study II

Patients were collected from the aforementioned database, which was supplemented with patients diagnosed with coeliac disease in year 2014. Study **I** showed that a majority of screen-detected patients were diagnosed after the year 2000, and because Study **II** focused on screen-detected patients, children diagnosed before the year 2000 were excluded. Also, those with missing information about clinical presentation at diagnosis or reason for coeliac disease suspicion were excluded. A total of 504 children with biopsy-proven diagnosis of coeliac disease by the Tampere University Hospital in 2000-2014 were included in the study.

9.3 Patients in Study III

Patients for Study **III** were found in the aforementioned paediatric coeliac disease database, supplemented by a diagnosis code search in the medical records of Tampere University Hospital. Patients were recognized according to the International Statistical Classification of Diseases and Related Health Problems (ICD) -10 diagnosis code (K90.0) for coeliac disease and earlier ICD-7–9 codes (579A, 579.0, 269.00, 269.98, 286.00) possibly indicating the disease. After the search, the total number of patients with suspected coeliac disease was 1070 (Figure 1 in the original publication **III**). Medical records of patients found by diagnosis code search were evaluated. A total of 20 patients were found to have an uncertain coeliac disease diagnosis, whereas in 26 cases coeliac disease was suspected but the diagnosis was not confirmed, and 63 had some other disease, for example haemophilia A, cow's milk allergy, lactose intolerance or von Willebrand disease. Six patients were deceased, with no further information available.

Thus, a total of 955 patients were found to have confirmed coeliac disease diagnosed in childhood, and 559 of them were 18 or older (as of 14 September 2016), were alive and had an available postal address. Study questionnaires were sent to these adult patients, and after two months, the 373 non-responders received the questionnaires again. A total of 237 (42%) patients answered the questionnaires (Figure 1 in the original publication **III**). The precise information about clinical presentation at childhood coeliac disease diagnosis was available for 236 patients, who comprised the final study cohort.

Based on the database information, those who answered the study questionnaires were more often females (69% vs 52%, $p<0.001$), had more coeliac disease in their first-degree relatives (56% vs 44%, $p=0.035$) and suffered type 1 diabetes less frequently than non-responders (9% vs 16%, $p=0.029$). The groups did not differ significantly in current age or age at the time of diagnosis, time of diagnosis, main clinical presentation of coeliac disease, presence of symptoms, growth disturbances or anaemia, body mass index or severity of villous atrophy at diagnosis.

9.4 Healthy controls

In Study **III**, 110 healthy adults were used as non-coeliac controls in a comparison of gastrointestinal symptoms and health-related quality of life with those of currently adult coeliac disease patients diagnosed in childhood. Non-coeliac controls were recruited with the help of coeliac disease patients from their neighbourhood and

friends. They did not have any suspicion of coeliac disease or coeliac disease in the family.

The median age of healthy controls was 49 (range 23-87) years, and 81% of them were females, which was significantly different from the characteristics of Study **III** coeliac disease patients (**Table 13**, page 77).

10 METHODS

10.1 Characteristics at diagnosis (Studies I-III)

Information about the clinical picture of coeliac disease at the time of diagnosis was collected from patient records, and in some cases, supplemented with interviews by a study physician or experienced study nurse. The time of coeliac disease diagnosis was defined as the date of the first small-bowel mucosal biopsy which confirmed the diagnosis. The presence and quality of possible symptoms was classified based on the data reported at the time of diagnostic evaluation.

Data were collected about age, gender, presence of gastrointestinal and extra-intestinal symptoms, growth disturbances, anaemia and other selected laboratory values, severity of small-bowel mucosal damage, family history of coeliac disease and possible co-morbidities such as type 1 diabetes, thyroidal diseases and Down's syndrome (Studies **I-III**).

In Study **I**, patients were divided into four groups according to age at the time of their coeliac disease diagnosis as follows: 1) infants (less than two years old); toddlers/pre-schoolers (two to seven years old); and school-aged (over seven years of age). Furthermore, patients were divided into four groups based on year of diagnosis: 1) 1966-1979, 2) 1980-1999, 3) 2000-2009 and 4) 2010-2013. Time periods were compared to describe possible changes in the clinical and histological features of coeliac disease first during the time of significant improvement in diagnostic methods and then in the twenty-first century.

10.1.1 Clinical presentation and severity of symptoms

The clinical picture of coeliac disease was divided into three groups based on the reason for coeliac disease suspicion and main clinical symptoms or signs recorded at diagnosis as follows: 1) gastrointestinal presentation, including abdominal pain, diarrhoea, vomiting and constipation; 2) extra-intestinal presentation such as arthralgia, neurologic and musculoskeletal symptoms, poor growth, dental enamel defects and laboratory abnormalities; and 3) screen-detected patients, who were

found in risk-group screening due to coeliac disease in the family or concomitant coeliac disease-associated condition such as type 1 diabetes or thyroidal disease. Furthermore, some patients had participated in the prospective Diabetes Prediction and Prevention or The Environmental Determinants of Diabetes in the Young studies, which included systematic screening for coeliac disease autoantibodies (Study **I**). In Studies **II** and **III**, the groups of gastrointestinal and extra-intestinal presentation were combined into one group of clinically detected patients.

The severity of clinical presentation in Study **I** was categorized as 1) no clinical symptoms or findings, 2) mild or occasional symptoms and normal growth, 3) moderate or more frequent symptoms and/or growth disturbances and 4) severe symptoms disturbing everyday life. In Study **II**, poor growth and anaemia were considered as findings. The severity of intestinal and extra-intestinal symptoms was classified, regardless of their presence, as 1) no symptoms, 2) mild symptoms, 3) moderate symptoms and 4) severe symptoms (Study **II**).

In Studies **II** and **III**, comparisons were made between screen-detected and clinically found patients and between the subgroups of asymptomatic and symptomatic screened patients.

10.1.2 Growth evaluation

Growth parameters were collected when available and compared to expected height, which is based on mid-parental height, and to sex- and age-related reference charts for height and weight (Studies **I-III**). These methods have been used for a long-time in clinical practice in Finland and have been demonstrated to improve the detection of growth disturbances associated with untreated coeliac disease (Nurminen et al. 2015, Saari et al. 2015). Poor growth was defined as an abnormal expected height and/or growth velocity (Studies **I-III**).

In Study **I**, patients were considered overweight according to the national guidelines if height-to-weight ratio was over 10% (<7 years old) or over 20% (≥7 years old). In Studies **II-III**, age- and sex-dependent standard deviation (SD) units and body mass index (BMI, weight/height^2, kg/m^2) were also calculated and compared between patient groups.

10.1.3 Laboratory parameters

Blood haemoglobin (Hb) values (g/l) were compared to age- and gender-dependent reference values (Fimlab, Haemoglobin), and anaemia was defined as decreased Hb at diagnosis or, if already treated with an iron supplement, before diagnosis (Studies **I-III**). Data were also collected about other iron markers such as mean corpuscular volume (reference value [Rf] 73-95 fl), plasma transferrin receptor (age and gender-dependent reference values [Fimlab, Transferrin receptor]) and plasma ferritin (Rf >20 mikrog/l). Furthermore, plasma albumin (Rf 36-48 g/l), plasma alanine aminotransferase (Rf ≤30 U/l) and plasma thyroid-stimulating hormone (Rf 0.27-4.20 mU/l) results were noted (Study **II**).

AGA and ARA testing was used in coeliac disease diagnostics in most cases in the 1970s-1990s, and, since then, EmA and tTGab testing has been increasingly utilized (**Figure 4**). Exact serum EmA and tTGab levels were collected (Studies **I-II**). In our settings, all EmA results were evaluated in the coeliac disease research centre by IFA by using human umbilical cord as a substrate. A dilution of 1:5 or more is considered positive and further diluted up to 1:4000 or until negative (Ladinser et al. 1994). Serum tTGab levels were measured in a hospital laboratory before 2011 using conventional ELISA (Phadia AB, Uppsala, Sweden) and after that by comparable automatized enzyme fluoroimmunoassay (Phadia). The upper limit for normal was considered 7 U/l and the highest reported value was 120 U/l.

Coeliac disease autoimmunity in Study **I** was defined as elevated TG2ab and/or EmA levels regardless of small-bowel biopsy results. This approach was selected to minimize the effects of subjective sampling and histopathologic interpretation of the intestinal biopsies to the incidence. In the twenty-first century, practically all children referred to the university hospital due to coeliac disease suspicion have been antibody-positive. Autoimmunity was estimated to show 10-20% higher numbers than biopsy-proven diagnoses: approximately 81% of seropositive children had previously been diagnosed after gastroduodenoscopy (Mäki et al. 2003).

10.1.4 Villous atrophy

In our study setting, the small-bowel mucosal structure was evaluated from duodenal biopsies, which were obtained using either upper gastrointestinal endoscopy or, before the year 1986, in some cases by Watson gastrointestinal biopsy capsule. At least four samples were taken from the distal duodenum, and from the year 2012 onwards also a minimum of two samples from the duodenal bulb (Husby et al. 2012). The severity of mucosal damage was assessed from several well-oriented biopsy

specimens by experienced pathologists, and the degree of villous atrophy was further classified as partial, subtotal or total, which corresponds to Marsh-Oberhuber grades IIIa-c (Dickson et al. 2006).

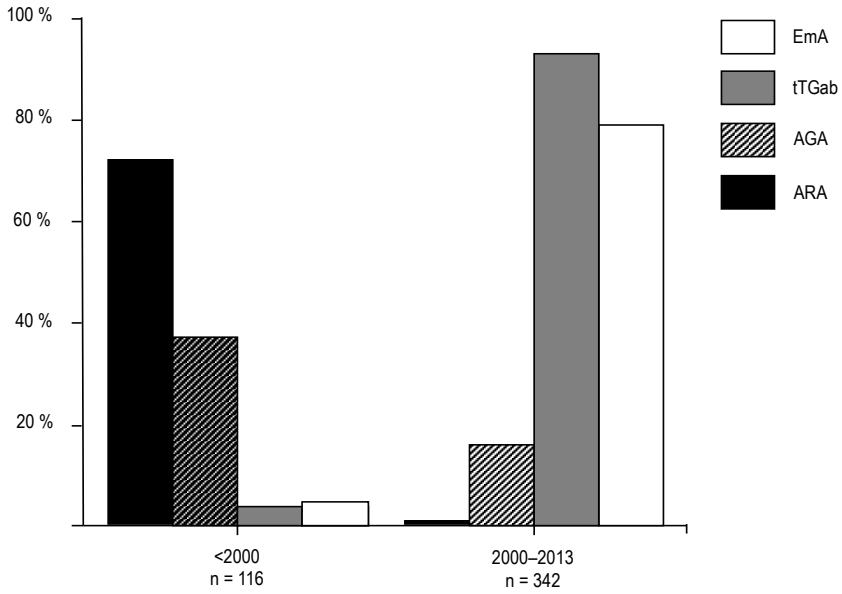

Figure 4. Use of different antibodies in coeliac disease diagnostics in children before the year 2000 and in 2000-2013 (Study **I**). AGA: anti-gliadin antibody; ARA: anti-reticulin antibody; EmA: endomysial antibody; tTGab: tissue transglutaminase antibody.

10.2 Short-term follow-up (Study II)

Routine follow-up visits of coeliac disease patients in our practice are arranged for approximately 3-6 and 10-12 months after a child has received the diagnosis. Furthermore, 120 children were evaluated for research purposes at a median of four years after diagnosis. Initiation of a gluten-free diet was advised for all patients and their families by a qualified dietitian, and after this, adherence and possible difficulties with the dietary treatment were evaluated during each follow-up visit. Data about the follow-up visits were mainly collected retrospectively.

In Study **II**, assessment of the strictness of the gluten-free diet was based on the self-reported avoidance of gluten and serological results, and it was classified as 1) strict, 2) occasional lapses or 3) no diet. Response to the dietary treatment was evaluated during follow-up visits based on the disappearance of symptoms and decrease in coeliac disease antibodies. The clinical and serological response in Study

II was categorized as good or no response. Furthermore, baseline tTGab results at diagnosis were compared to follow-up values, which were measured at a median of 13 (range 6-24) months after diagnosis on a gluten-free diet (Study **II**).

10.3 Long-term follow-up in adulthood (Study III)

Adult patients who were diagnosed with confirmed coeliac disease in childhood were invited to answer long-term follow-up questionnaires. The questionnaires evaluated patients' current health, dietary treatment, quality of life and possible ongoing symptoms.

10.3.1 Study questionnaire

A specific study questionnaire was used to evaluate current sociodemographic characteristics, family relations, lifestyle, common health and treatment of coeliac disease (Study **III**). Patients were asked to report on their work and study situation, presence of children and coeliac disease in the family, comorbidities, membership of a coeliac society, smoking, and regularity of physical exercise. Also, height and weight were asked for and BMI (kg/m^2) calculated. Patients answered questions concerning their experienced health, which was categorized as 1) excellent, 2) good, 3) moderate or 4) poor; and health concerns were classified as 1) none or minor or 2) moderate or severe. Patients described any current symptoms they believed to be caused by coeliac disease and whether the dietary treatment caused restrictions in daily life. They were asked about their adherence to a gluten-free diet, and their answers were categorized as 1) strict, 2) occasional lapses, 3) regular lapses (every week to once a month) or 4) no diet. Patients described also their motivation and difficulties regarding the diet. Reported long-term follow-up was classified as 1) regular or 2) none or occasional.

10.3.2 Psychological General Well-Being questionnaire

The Psychological General Well-Being (PGWB) questionnaire was used in Study **III** to evaluate self-perceived health-related quality of life (Dimenäs et al. 1996). It comprises 22 questions that assess experiences of anxiety, depression, positive well-being, self-control, general health and vitality. Each question is graded from 1 to 6,

with higher scores representing better well-being. The total score is calculated as a sum of all scores, from 22 to 132, and the subdimensions are calculated as sums of scores of selected questions. The PGWB questionnaire has been widely used in studies evaluating coeliac disease patients (Mustalahti et al. 2002, Viljamaa et al. 2005a, Ukkola et al. 2011, Mahadev et al. 2016).

10.3.3 Gastrointestinal Symptom Rating Scale

Patients answered the Gastrointestinal Symptom Rating Scale (GSRS) questionnaire to clarify their current gastrointestinal complaints and their severity (Study **III**; Revicki et al. 1998). The questionnaire consists of 15 questions scored from 1 to 7, higher scores representing more difficult and frequent symptoms. The total score is the mean of all scores, and the subdimensions are calculated as the means of selected questions to evaluate more precisely how the patients experience the most common gastrointestinal symptoms: abdominal pain, indigestion, constipation, diarrhoea and reflux.

10.4 Statistical analysis (Studies I-III)

In all studies, categorical variables were expressed as percentages, and in Study **III** also as numbers. Non-parametric numeric data were described as medians with an interquartile range. Comparison of categorized values was done in cross-tabulation with χ^2 or Fisher's exact test, and non-parametric numeric values were compared either using the Mann-Whitney U or Kruskal-Wallis test.

In Study **I**, the annual incidence rate (cases/100,000/year) of coeliac disease autoimmunity was calculated by dividing the number of seropositive children by the number of at-risk children, which was estimated to be between 119,243 and 121,581 in our hospital catchment area in 2001-2013. Secular trends in annual incidence rate were reported as incidence rate ratios with 95% confidence intervals calculated using Poisson regression. Furthermore, in Study **II**, age differences between the groups were adjusted using binary logistic regression, and in Study **III**, pair-wise post hoc comparisons were conducted using Bonferroni correction.

A P value of <0.05 was considered statistically significant. Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) versions 22

and 23 (IBM Corporation, Armonk, New York, USA) and Stata version 13 (StataCorp LP, College Station, Texas, USA).

10.5 Ethical considerations (Studies I-III)

The ethical guidelines of the Declaration of Helsinki (1975) were followed in all studies. The research protocols were approved by the Paediatric Clinic of Tampere University Hospital, and when patients were contacted, also by the Regional Ethics Committee of Tampere University Hospital (R05183, R11187, R16091). All study subjects and/or their parents answering the study questionnaires or participating in the prospective study enrolment or personal interviews gave written informed consent.

11 RESULTS

11.1 Clinical picture of paediatric coeliac disease (Study I)

Age at coeliac disease diagnosis rose significantly from a median of 4.3 (interquartile range, IQR 1.2, 10.6) years before 1980 to 7.6-9.0 (IQR 3.0, 14.4) years in 1980-2013, and, concurrently, the percentage of patients diagnosed in infancy decreased (**Table 9**). The percentages of screen-detected and asymptomatic patients increased, whereas gastrointestinal and extra-intestinal presentations as a main clinical finding declined, and the severity of clinical presentation became milder after the 1990s, with the changes remaining stable in 2000-2013 (**Table 9**). Concurrently, poor growth became rarer, but this trend still continued in the twenty-first century, whereas there was no difference in the percentage of overweight or obese patients between 2000-2009 and 2010-2013 (**Table 9**). The presence of anaemia was lowest and the median Hb value highest (127 [IQR 119, 133] g/l) in 2000-2009 compared with other time periods (median 122-125 [IQR 110-132] g/l) (**Table 9**).

The severity of mucosal atrophy became milder at the turn of the twenty-first century, and the change subsequently levelled off (**Table 9**). EmA median values remained at the same level in 2000-2013 (1:500 [IQR 1:100, 1:1000] vs 1:500 [IQR 1:100, 1:1250], p=0.860, not analysed before 2000). There were no significant differences between the time periods in the gender distribution or the presence of comorbidities (**Table 9**).

11.1.1 Patients with gastrointestinal presentation

Gastrointestinal presentation was the main finding at diagnosis in 49% of children diagnosed during the entire study period. When these patients in the four different time periods were compared, median age at diagnosis rose from 4.4 (IQR 1.1, 12.1) years before the 1980s, to 7.0-7.8 (IQR 2.0, 12.7) years in 1980-2013. Patients with gastrointestinal symptoms were younger than all study patients as a group, except before the 1980s. The presence of diarrhoea and vomiting decreased, and abdominal pain and constipation increased when comparing the time before and after the year

2000 (Table 2 in original publication **I**). As in all study patients, the severity of the disease and villous atrophy became milder also in patients with a gastrointestinal presentation (Table 3 in original publication **I**). The same trends in the histology and the severity of the clinical presentation were also seen in a subgroup of patients with diarrhoea (data not shown).

Table 9. Clinical and histological presentation of children diagnosed with coeliac disease during different time periods.

	1966-1979 n=46	1980-1999 n=69	2000-2009 n=318	2010-2013 n=163	P value
Girls, %	67	59	61	71	0.125
Age <2 years, %	37	15	3	3	<0.001
Clinical presentation, %					<0.001
Gastrointestinal	59	59	49	50	
Extra-intestinal	36	36	21	24	
Risk-group screened	5	4	31	26	
Severity of clinical presentation, %					<0.001
Asymptomatic	0	2	12	14	
Mild	23	40	39	51	
Moderate	66	53	44	32	
Severe	11	6	5	3	
Anaemia, %	23	23	14	26	0.014
Poor growth, %	66	36	34	23	<0.001
Overweight or obese, %	ND	ND	10 [a]	14 [b]	
Type 1 diabetes, %	2	10	8	9	0.455
Thyroidal disease, %	7	4	2	1	0.076
Down syndrome, %	2	3	1	1	0.394
Degree of villous atrophy, %					<0.001
Partial	10	14	42	38	
Subtotal	48	33	40	42	
Total	43	53	19	20	

Data were available for >80% of patients, except in: [a] 133 and [b] 99. ND: no data.

11.1.2 Incidence of coeliac disease autoimmunity

The annual incidence of coeliac disease autoimmunity at the paediatric gastroenterology clinic of Tampere University Hospital was 31/100,000 in the year 2001 and increased gradually, reaching a peak of 57/100,000 in the year 2007. After this, the incidence fluctuated between 34 and 53/100,000/year (Figure 2 in original publication **I**).

11.2 Screen-detected patients (Studies II-III)

11.2.1 Clinical features at diagnosis

A total of 145 (29%) of all children diagnosed with coeliac disease in 2000-2014 were found due to risk-group screening and 359 (71%) due to clinical suspicion (Study **II**). Of currently adult study patients, 48 (20%) were found by screening and 188 (80%) due to clinical suspicion in childhood (Study **III**). The main reasons for screening were type 1 diabetes, coeliac disease in relatives and participation in prospective follow-up studies because of genetic predisposition for type 1 diabetes (**Table 10**). Type 1 diabetes and coeliac disease in the family were also significantly more common in screen-detected children than in those clinically found (**Table 11**).

Table 10. Reasons for coeliac disease evaluations in 145 screen-detected children (Study **II**).

Reason for screening	%
Coeliac disease in a first-degree relative	35
Coeliac disease in more distant relative	19
Type 1 diabetes	19
Children participating in prospective birth cohort studies (DIPP/TEDDY)	19
Other	8

DIPP: Diabetes Prediction and Prevention; TEDDY: The Environmental Determinants of Diabetes in the Young.

Screen-detected and clinically found patients did not differ in demographic data at diagnosis or year of diagnosis (Study **II**), but when currently adult patients were compared (Study **III**), those that were screen-detected were significantly older and diagnosed in more recent years compared with those found due to clinical suspicion (**Table 11**).

Also, 44-52% of screen-detected children suffered from previously unrecognized symptoms at diagnosis, although these symptoms were less severe than those in clinically found patients (Figure 1B in original publication **II**). In the comparison of specific symptoms, diarrhoea was more common among clinically detected (42% vs 29%, p=0.045), whereas the groups did not differ in the presence of abdominal pain, constipation, skin symptoms or arthralgia (Table 2 in original publication **II**). Poor growth and anaemia were more common in clinically found children, although these findings were observed also in a significant proportion of screen-detected patients (**Table 11**). Furthermore, blood Hb and serum albumin levels were lower in patients found due to clinical suspicion, whereas there were no differences in other laboratory results, including median EmA titres and anthropometric measurements (Table 3 in original publication **II**). Also, the degree of histological damage was comparable in the different groups (**Table 11**).

Asymptomatic children were older and had lower EmA levels and higher median Hb values at diagnosis than symptomatic screened patients. However, the differences in EmA and Hb levels were no longer significant after the groups were adjusted for age (Table 4 in original publication **II**). The subgroups did not differ in gender distribution, presence of anaemia, growth parameters, other laboratory results, coeliac disease in relatives, concomitant type 1 diabetes or degree of mucosal villous atrophy (Table 4 and Figure 3A in original publication **II**).

Table 11. Characteristics of patients with childhood coeliac disease diagnosis in Study **II,** including those diagnosed in 2000-2014, and in Study **III** including currently adult patients.

	Study II (children)			Study III (currently adults)		
	Screen-detected n=145	**Clinically found n=359**	**P value**	**Screen-detected n=48**	**Clinically found n=188**	**P value**
Girls, %	62	67	0.336	69	69	0.957
Age, median (IQR), years	7.0 (4.1, 11.7)	8.0 (5.0, 11.7)	0.202	11.7 (8.1, 14.6)	8.7 (4.5, 13.3)	0.004
Year of diagnosis, median (IQR)	2008 (2007, 2012)	2009 (2006, 2012)	0.786	2000 (1992, 2005)	1997 (1983, 2003)	0.017
Any symptoms, %	52	92	<0.001	44	86	<0.001
Anaemia, %	7	23	<0.001	19	31	0.091
Poor growth, %	16	37	<0.001	17	52	<0.001
Type 1 diabetes, %	22	2	<0.001	28	3	<0.001
Thyroidal disease, %	1	2	1.000	10	7	0.742
Down syndrome, %	0	1	0.314	0	0	-
Degree of villous atrophy, %			0.265			0.176
Partial	45	37		34	31	
Subtotal	39	42		48	37	
Total	17	21		18	32	
Coeliac disease in family, %	60 [a]	34 [b]	<0.001	ND	ND	-

Data were available for >85% of patients, except in: [a] 92 and [b] 213. IQR: interquartile range; ND: no data.

11.2.2 Short-term follow-up (Study II)

Adherence to a gluten-free diet on average one year (median time of follow-up 13 months) after the coeliac disease diagnosis was better in screen-detected than in clinically found children (91% vs 83% respectively, p=0.047), whereas there was no difference between symptomatic and asymptomatic screen-detected patients (93% vs 93%, p=1.000). Strict dietary adherence was as common in those with and without coeliac disease in the family (81% vs 90%, p=0.060) and in those with and without concomitant type 1 diabetes (86% vs 85%, p=0.835).

The clinical and serological response to the treatment was excellent and similar in both screen- and clinically detected children (98% vs 96%, p=0.766). Distribution of tTGab values at diagnosis and on a gluten-free diet were also comparable, and a decrease in these values was seen similarly in both groups (**Table 12** and Figure 2 in original publication **II**).

Table 12. Tissue transglutaminase antibody (tTGab) levels at coeliac disease diagnosis and after 6-24 months on a gluten-free diet in screen-detected (n = 74) and clinically detected (n = 176) children in Study **II.**

	At diagnosis, % [a]		On a gluten-free diet, % [b]	
tTGab, U/l	**Screen-detected**	**Clinically detected**	**Screen-detected**	**Clinically detected**
<7	1	3	69	69
7–119	49	37	28	31
≥120	50	60	3	0

P values calculated using Fisher's exact test: [a] 0.214 and [b] 0.150.

11.2.3 Long-term health (Study III)

Currently adult patients answering the questionnaires were diagnosed with coeliac disease a median of 18.5 (IQR 12.7, 30.7) years earlier in childhood. Screen-detected patients had more coeliac disease in first-degree relatives and more concomitant type 1 diabetes and were less often current smokers than those found because of clinical suspicion (**Table 13**). The groups did not differ in their current age, presence of other comorbidities or children, physical activity, body mass index or earlier smoking (**Table 13**). Screened and clinically detected patients were also comparable in work and studying status (full-time work: 68% vs 62% and p=0.530; students: 40% vs 31%

Table 13. Health and lifestyle characteristics in currently adult patients diagnosed with coeliac disease in childhood (Study **III**).

	Screen-detected n=48	**Clinically found n=188**	**P value**
Age, median (IQR) years	26.6 (21.1, 35.2)	27.2 (22.1, 38.1)	0.328
Presence of children, %	38	44	0.416
Regular physical exercise, [a] %	60	59	0.863
BMI, median (IQR), kg/m^2	24.6 (22.2, 26.7)	23.4 (21.3, 26.6)	0.198
Currently smoking, %	4	15	0.042
Had quit smoking, %	21	22	0.921
Coeliac disease in the family, %	65	40	0.002
Comorbidities, %			
Type 1 diabetes	27	3	<0.001
Thyroidal disease	17	8	0.103
Other GI disease	2	8	0.317
Rheumatic disease	0	4	0.366
Hypertension	9	4	0.242
Dermatological disease	13	17	0.488
Asthma	9	12	0.484
Allergy	47	41	0.453
Eating disorder	0	5	0.210
Depression	11	14	0.583
Possible complications, %			
Fracture(s)	31	22	0.180
Osteoporosis	0	2	0.290
Miscarriage(s)	7	8	1.000
Malignancy [b]	0	2 [a]	0.584

[a] Defined as more than three times per week.
[b] For example lymphoma, brain and breast cancer.
BMI: body mass index; IQR: interquartile range.

and p=0.281). Results were similar when evaluated in the subgroups of asymptomatic and symptomatic screen-detected patients (Table 4 in original publication **III**).

A total of 21% of the screen-detected and 24% of the clinically detected patients reported persistent symptoms possibly related to coeliac disease (p=0.627). This was seen also in 22% of the originally asymptomatic screened patients. Screen-detected patients had higher scores in GSRS abdominal pain and reflux than non-coeliac controls, indicating more severe symptoms, whereas there were no differences in total, indigestion, diarrhoea or constipation scores between screen-detected coeliac disease patients, clinically detected patients and controls (Figure 2B in original publication **III**). There were no significant differences in current GSRS scores between the subgroups of originally symptomatic and asymptomatic screen-detected patients (data not shown).

11.2.4 Treatment in adulthood (Study III)

Screen-detected and clinically found patients did not differ in long-term adherence to a gluten-free diet (**Figure 5A**), and they experienced the diet as equally easy to follow (mostly easy: 79% vs 78%; p=0.846). Dietary adherence was comparable also between asymptomatic and symptomatic screen-detected patients (Table 4 in original publication **III**). Both screen- and clinically detected patients considered it important to maintain a strict diet to avoid long-term complications (85% vs 84%, p=0.748) and symptoms (67% vs 73%, p=0.353). The use of gluten-free oats as part of their diet did not differ between the groups (98% vs 94%, p=0.468). Reported attendance at regular visits to follow up on coeliac disease (29% vs 24%, p=0.467) was also comparable between the groups, but screen-detected patients were less often members of a coeliac society (38% vs 57%, p=0.019).

11.2.5 Quality of life and experiences of the disease (Study III)

Self-perceived general health did not differ between screen- and clinically detected patients (**Figure 5B**), or between the subgroups of asymptomatic and symptomatic screened patients (Table 4 in original publication **III**). Furthermore, screen-detected and clinically found patients were comparable as regards current health concerns (none/minor: 89% vs 80% respectively, p=0.137) and experience of daily life restrictions caused by the dietary treatment (47% vs 47%, p=0.965).

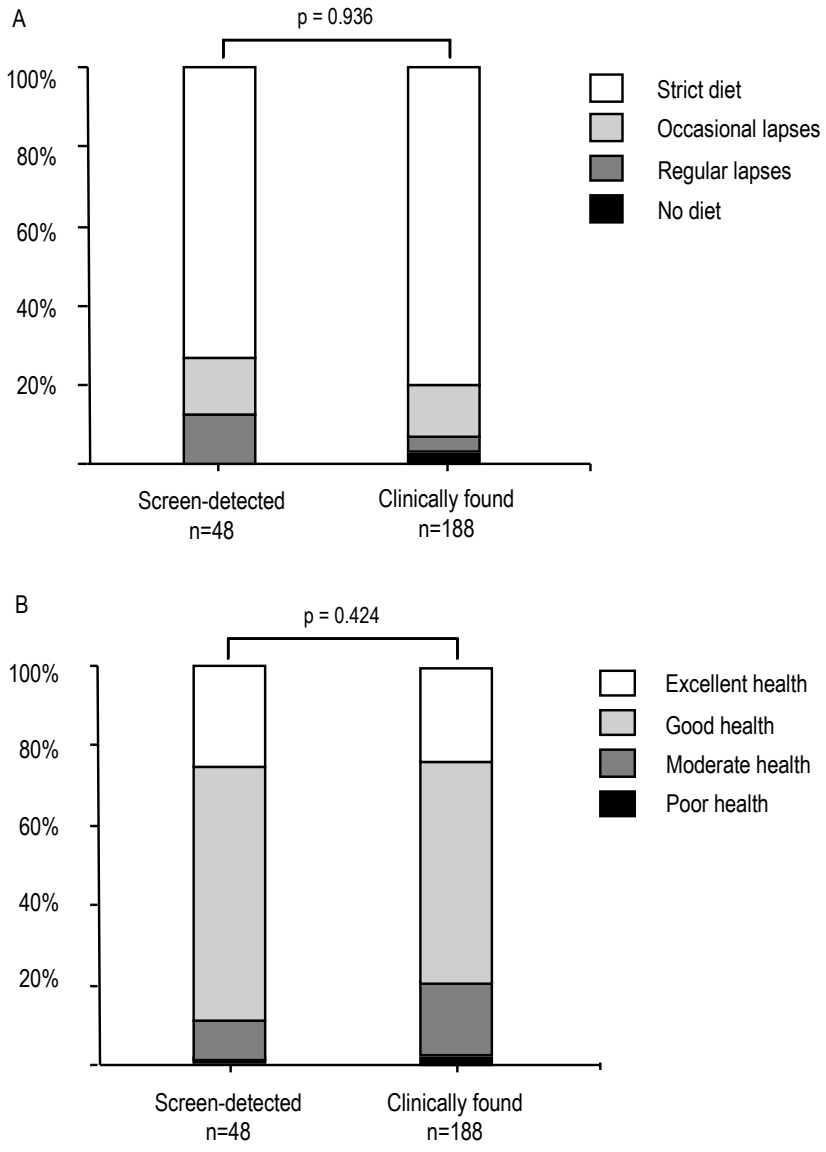

Figure 5. Adherence to gluten-free diet (A) and self-perceived experience of general health (B) in screen-detected and clinically found currently adult patients diagnosed with coeliac disease in childhood.

In the PGWB, total and anxiety scores were lower in asymptomatic screened patients than in non-coeliac controls, indicating a poorer overall quality of life and increased anxiety, whereas both asymptomatic and clinically found coeliac disease patients had less of an experience of vitality than those without coeliac disease (**Table 14**). Otherwise there were no significant differences in the health-related quality of life between the asymptomatic or symptomatic screen-detected or clinically found coeliac disease patients and non-coeliac controls (**Table 14**).

Table 14. Median (interquartile range) Psychological General Well-Being scores in currently adult patients diagnosed with coeliac disease in childhood and in non-coeliac controls (Study **III**).

	Screen-detected		Clinically found n=188	Controls n=110
	Asymptomatic n=27	Symptomatic n=21		
Total score	98 (84, 114)*	109 (102, 113)	106 (93, 113)	107 (100, 114)
Reduced anxiety	21 (18, 24)*	25 (22, 27)	24 (20, 26)	25 (22, 27)
Reduced depression	17 (14, 18)	17 (16, 18)	17 (15, 18)	17 (15, 18)
Positive well-being	17 (14, 20)	19 (16, 21)	18 (15, 19)	17 (15, 19)
Self-control	15 (13, 17)	16 (16, 17)	16 (14, 17)	16 (14, 17)
General health	15 (13, 16)	15 (12, 16)	14 (11, 16)	15 (13, 16)
Vitality	15 (13, 20)*	18 (16, 19)	17 (15, 19)*	19 (17, 20)

*Statistically significant difference (p value <0.05) when compared with non-coeliac controls.

12 DISCUSSION

12.1 Temporal changes in paediatric coeliac disease

Study **I** showed that the most significant changes in the clinical and histological presentation of coeliac disease occurred as early as the 1980s and 1990s, and thereafter most of these shifts reached a plateau in 2000-2013. The changes in presentation are in line with previous findings from other developed countries, but compared with Finland, they seemed often to occur later and still continue (Garampazzi et al. 2007, McGowan et al. 2009, Roma et al. 2009, Whyte et al. 2013, Gokce and Arslantas 2015, Tapsas et al. 2016, Almallouhi et al. 2017), except severity of villous atrophy, which remained unchanged in Turkey in 2005-2012 (Gocke et al. 2015). After our study was published, Beitnes and colleagues (2016) also reported a relatively stable clinical and histological presentation of paediatric coeliac disease in the twenty-first century in Norway.

12.1.1 Clinical and histological characteristics

Screening for coeliac disease in at-risk groups increased sixfold after the 1990s. At the same time, the proportions, but not the total numbers, of patients with gastrointestinal and extra-intestinal manifestations decreased, and gastrointestinal presentation shifted away from the previously common diarrhoea and vomiting towards abdominal pain and constipation. Other studies have similarly described changes in the clinical picture from "classical" to "atypical" and screen-detected (Garampazzi et al. 2007, McGowan et al. 2009, Roma et al. 2009, Whyte et al. 2013, Gokce and Arslantas 2015, Tapsas et al. 2016, Almallouhi et al. 2017), although the definitions for the terms have varied noticeably (**Table 2**, page 40).

The changes in clinical presentation appear to be have started in different times and occur at different paces in different countries; the levelling off in the changes has been reported only in Finland and Norway (Beitnes et al. 2016). However, some of the previous studies did not evaluate trends or possible plateaus in the changes in the twenty-first century, but instead focused on comparing the presentation before

and after the year 2000 (McGowan et al. 2009, Whyte et al. 2013). Nevertheless, in the majority of developed countries and especially in developing countries (Rawal et al. 2010), the clinical presentation of coeliac disease is evidently still changing.

The increase in screening for coeliac disease after the 1990s probably also explains part of the milder clinical presentation and increased number of asymptomatic patients. A comparable trend has been reported in other countries (McGowan et al. 2009, Roma et al. 2009, Whyte et al. 2013). However, in our settings, the overall severity of clinical presentation became milder already in 1980-1990 and, for example, growth disturbances decreased steadily during the entire study period. The beginning of the change probably lies even earlier, when a similar finding towards milder clinical features was published by Mäki and colleagues as early as 1988 in children diagnosed with coeliac disease in the 1960-1980s in Finland.

Although the severity of mucosal damage became milder and then levelled off simultaneously as screening increased, screening cannot be the only explanation for the less severe histology. This change was also seen among patients with a gastrointestinal presentation, and, in Studies **II** and **III**, the degree of villous atrophy was not associated with clinical presentation.

It is possible that improved diagnostic methods have, apart from enabling risk-group screening, also lowered the threshold for case-finding. This together with increased knowledge about the various features of coeliac disease could have resulted in earlier diagnoses with milder presentations (McGowan et al. 2009, Roma et al. 2009, Whyte et al. 2013).

12.1.2 Role of environmental factors

Over one-third of the patients in Study **I** were under two years old at the time of diagnosis before the 1980s, but thereafter both the proportion and number of these youngest patients decreased significantly. A similar change has been reported from Greece and Sweden (Roma et al. 2009, Namatovu et al. 2014). There, the overall incidence of coeliac disease in children has increased in the twenty-first century, but in recent years almost none of the patients were diagnosed in early infancy (Roma et al. 2009, Namatovu et al. 2014). The disappearance of these youngest patients suggests that, in addition to the above-mentioned changes in diagnostic approach, there has been a true change in the phenotype of coeliac disease towards older age at disease onset. The change has occurred so rapidly that genetic factors could hardly explain all of it, and there might be a marked role played by environmental factors.

Further support for the role of an environmental effect comes from the concomitant change in the true incidence of coeliac disease and type 1 diabetes over the past few decades (Lohi et al. 2007). Although the evaluation of coeliac disease autoimmunity in the present study was limited to the most recent decades and patients found in clinical practice, the observed plateau in what was previously an increasing incidence occurred remarkably parallel with the levelling off in the recently reported incidence of type 1 diabetes (Berhan et al. 2011, Harjutsalo et al. 2013). Also, a similar phenomenon has been detected in the incidences of inflammatory bowel diseases and asthma (Agnarsson et al. 2013, Henriksen et al. 2015), although in Finland inflammatory bowel diseases have still became more common (Virta et al. 2017).

"The hygiene hypothesis" was invented based on the idea that the exposure to infectious agents may protect against allergic diseases (Strachan 1989). This hypothesis has later been used to attempt to explain the increase in prevalence of also other immune-mediated diseases, such as coeliac disease and type 1 diabetes, an increase that has occurred concurrently with declining infections and "cleaner" environments in developed countries (Lohi et al. 2007, Harjutsalo et al. 2008, Kondrashova et al. 2013). Differences in the prevalence of these diseases have also been reported between closely related countries, i.e. Finland and Russian Karelia, whose populations have comparable genetic backgrounds and a similar use of gluten, but different hygienic environments (Kondrashova et al. 2005, Kondrashova et al. 2008).

Viral infections may alter the tolerance of dietary antigens (Bouziat et al. 2017), and gastrointestinal and/or respiratory infections during infancy and neonatal period have indeed been associated with an increased risk of developing coeliac disease (Welander et al. 2010, Myléus et al. 2012a, Canova et al. 2014, Mårild et al. 2015, Auricchio et al. 2017, Kemppainen et al. 2017b). Another factor which could modify this risk is the use of antibiotics, but the data have been inconsistent (Mårild et al. 2013, Canova et al. 2014, Kemppainen et al. 2017a). Vaccinations do not seem to increase the risk of coeliac disease (Myléus et al. 2012b), and the rotavirus vaccination may even play a protective role (Kemppainen et al. 2017b). The effects of infections and their treatments on the risk of developing coeliac disease are complex; a possible interaction between concomitant infections, discontinued breastfeeding and gluten introduction has also been discussed (Myléus et al. 2012a, Kemppainen et al. 2017b).

Interest in the significance of nutritional factors in infancy was roused after the incidence of coeliac disease in Swedish infants abruptly increased fourfold after changes in national feeding recommendations and a concurrent increase in gluten

content in commonly used food products in 1984-1996 (Ivarsson et al. 2000). After this, the importance of breast-feeding and the best practices in introducing gluten into the diet in early childhood have been studied in several randomized and observational studies (Størdal et al. 2013, Vriezinga et al. 2014, Lionetti et al. 2014, Jansen et al. 2014, Aronsson et al. 2015, Aronsson et al. 2016). The current accepted conclusion is that the duration of breastfeeding does not affect the risk of developing coeliac disease, and the risk is also unaltered if gluten is introduced into the diet between four and twelve months of age, although earlier introduction may result in earlier development of the disease. Large amounts (approximately 1 g per day) of gluten in the diet are recommended avoided during infancy (Aronsson et al. 2016, Szajewska et al. 2016). Also, other dietary factors such as the use of vegetables, oils and sweet drinks could play a role in the pathogenesis (Barroso et al. 2018).

Other environmental factors which have been proposed as playing a role in the development of coeliac disease are, for example, different maternal and perinatal factors such as foetal growth, diseases and diet of the mother, season and region of birth, and birth delivery mode (Mårild et al. 2012, Canova et al. 2014, Størdal et al. 2014, Emilsson et al. 2015, Namatovu et al. 2016, Unalp-Arida et al. 2017, Koletzko et al. 2018). Many environmental factors also alter the intestinal microbiota, which recently has been of great interest in the research into coeliac disease pathogenesis (Cenit et al. 2015). Microbiota seems to differ between both treated and untreated coeliac disease patients and healthy controls, but whether this is a cause or a consequence of the disease is not known (Collado et al. 2009, Di Cagno et al. 2011). There is also some evidence that the microbiota could be associated with the clinical features of coeliac disease (Wacklin et al. 2013).

12.2 Coeliac disease-associated complications and prognosis

The degree of small-bowel mucosal damage and levels of disease-specific antibodies may reflect the activity of coeliac disease and could thus be associated with the risk of developing complications. Histopathologic findings and antibody levels were comparable in screen-detected and clinically found patients in Studies **II** and **III.** Also, asymptomatic children could present with advanced mucosal atrophy, although their EmA values were lower than in symptomatic patients. These results are in line with previous studies showing a poor association between clinical presentation and the histological severity of coeliac disease (Brar et al. 2007, Jatla et al. 2009, Thomas et al. 2009, Dorn et al. 2010). Taavela and colleagues (2013a) report

significant correlations between GRSR and PGWB scores and mucosal damage in adult patients, but the correlation coefficients are quite low. The lack of association between symptoms and histological damage has been suggested as related to the varying length of the small-intestinal lesion (Weizman et al. 1997), but later evidence does not support this (Murray et al. 2008).

The development of coeliac disease-related complications such as anaemia, impaired growth and decreased bone accrual could be used to describe the progress of the disease in children. The presence of anaemia has been shown to be associated with more severe form of histological coeliac disease (Thomas et al. 2009, Abu Daya et al. 2013, Rajalahti et al. 2016), whereas the association between growth and the degree of histological damage is more controversial (Weizman et al. 1997, Jatla et al. 2009, Nurminen et al. 2015). In Studies **II** and **III**, anaemia and growth disturbances were less common in screen-detected than in clinically found patients, but it is remarkable that even some of the otherwise asymptomatic patients suffered from these findings. Similar results about the presence of complications also in screen-detected children have been reported in other studies (Korponay-Szabó et al. 2007, Turner et al. 2009, Nurminen et al. 2015, Rajalahti et al. 2016, Björck et al. 2017). It is evident that the absence of symptoms does not rule out the possibility of these complications.

A less frequent prevalence of anaemia and growth disturbances in screen-detected patients could indicate that diagnosis was made at an earlier stage of the disease than in the clinically found patients. However, the natural course of coeliac disease and the risk of developing complications at the individual level are very difficult to predict (Verkasalo et al. 2005, Matysiak-Budnik et al. 2007, van Koppen et al. 2009, Choung et al. 2017). It has been suggested that asymptomatic patients may have less severe disease than clinically found patients, and further evidence from long-term prospective follow-up studies has been requested about their risk of developing complications (Chou et al. 2017). However, villous atrophy seems not to be associated with clinical presentation (Brar et al. 2007, Jatla et al. 2009, Thomas et al. 2009, Dorn et al. 2010), and even the classification of patients based on the presence of symptoms is unreliable (Ukkola et al. 2011, Kinos et al. 2012, Agardh et al. 2015). This indicates that factors other than the presence or absence of symptoms before diagnosis would be a better indicator for the long-term prognosis of coeliac disease.

Although the follow-up time in Study **III** was exceptionally long compared with previously published studies, most of its participants were still quite young of age. This hampers evaluation of the slowly developing co-morbidities and complications

of coeliac disease. Furthermore, because all patients were diagnosed in childhood and adhered well to a gluten-free diet, the effects of untreated coeliac disease could not be evaluated in the present study.

Currently, most coeliac disease patients remain unrecognized, and whether they are at risk of severe or even permanent complications is not known (Korponay-Szabó et al. 2007, Turner et al. 2009, Nurminen et al. 2015, Rajalahti et al. 2016, Björck et al. 2017). Diagnostic efficiency could be increased by targeted screening of at-risk groups or even the entire population, but this should be balanced with consideration of the possible harms of the treatment, especially for those asymptomatic patients who may have felt themselves healthy before their diagnosis.

12.3 Special features of screen-detected patients

12.3.1 Dietary adherence

We found screen-detected patients to be comparable to clinically found patients in their adherence to a gluten-free diet, both in the short-term follow-up a few years after diagnosis in Study **II** and in adulthood in Study **III**. Several earlier studies have evaluated dietary adherence in children diagnosed with coeliac disease (**Table 8**, pages 57-58), but the follow-up time in most of these studies is relatively short: less than ten years. Furthermore, only a limited number of studies have investigated the association between clinical presentation at diagnosis and dietary adherence (Fabiani et al. 2000, Roma et al. 2010, Kinos et al. 2012, Kurppa et al. 2012). In earlier Finnish studies, the diagnostic approach was not associated with the strictness of the diet (Kinos et al. 2012, Kurppa et al. 2012). On the contrary, Fabiani et al. (2000) from Italy found that only 23% of screen-detected adolescents adhere to dietary treatment, compared with 68% of those found due to clinical symptoms, whereas Roma et al. (2010) from Greece reported screen-detected patients adhering to the diet even better than paediatric patients as a whole (88% vs 58%). The study by Fabiani et al. (2000) was published over a decade ago. Since then, gluten-free products have become more available, likely also facilitating maintenance of the diet (Newberry et al. 2017); better adherence numbers have been published for Italian adolescents (Altobelli et al. 2013).

Aside from the above-mentioned paediatric studies, some adult studies have reported that clinical presentation of coeliac disease at diagnosis does not affect

dietary adherence (Paavola et al. 2012, Mahadev et al. 2016). However, only a small percentage of patients in these studies were diagnosed in childhood, and they were not evaluated separately. Whether paediatric coeliac disease patients should be investigated as a separate group remains unclear. The issue is scarcely studied but, based on the findings from Högberg et al. (2003), the diet could be easier to take as a part of everyday life if it is initiated in early childhood. However, the transition phase to adulthood is a particularly important period for those patients diagnosed in childhood taking responsibility for their dietary treatment (Ludvigsson et al. 2016). Furthermore, especially if the diagnosis has been made at a young age, patients may not remember their symptoms before the diagnosis, and the reasons for a gluten-free diet might be unclear to the paediatric patients themselves. This could predispose them to poorer motivation to adhere to the diet later in life.

Thus far only two previous studies have specifically evaluated the long-term follow-up and transition of paediatric coeliac disease patients to adulthood. O'Leary et al. (2004) reported that only 50% of Irish patients followed a gluten-free diet 28 years after childhood diagnosis, whereas Högberg et al. (2003) reported the adherence of Swedish patients to be 36-80% 17-24 years after the diagnosis. It is unclear whether any screen-detected patients were included in these studies.

The variable results suggest that there are probably also factors other than clinical presentation affecting dietary adherence. The strictness of adherence has been associated, for example, with diagnostic and current age, implementation and type of follow-up, social relationships, educational level of parents and knowledge about coeliac disease (Jadresin et al. 2008, Wagner et al. 2008, Chauhan et al. 2010, Errichiello et al. 2010, Roma et al. 2010, Mozer-Glassberg et al. 2011, Kurppa et al. 2012, Charalampopoulos et al. 2013, Barnea et al. 2014, Garg and Gupta 2014, MacCulloch and Rashid 2014). Reasons reported for non-adherence by patients have been poor availability, high prices and inadequate labelling of gluten-free products, and that the patients experienced the diet as being too restrictive (Olsson et al. 2008, Lee et al. 2012, Ukkola et al. 2012, MacCulloch and Rashid 2014, Taghdir et al. 2016).

It is likely that the aforementioned variations in follow-up and ease of maintaining a gluten-free diet between countries and time periods explain some of the differences between the present and previously published studies in reported dietary adherence. For example, in Finland, children with a biopsy-proven diagnosis of coeliac disease receive financial compensation from the government until they reach the age of 16, and a similar approach was previously applied also to adults (Coeliac disease, Current Care Guidelines 2010). This could have a positive effect on the adherence to a gluten-free diet, although a comparable compensation system has been implemented

in Italy as well, where dietary adherence varies significantly (Fabiani et al. 2000, Tommassini et al. 2004, Bellini et al. 2011, Altobelli et al. 2013).

The present study showed that also screen-detected patients can achieve good long-term adherence to the diet in a country with a good accessibility and knowledge of gluten-free products. This is important, because although we could in theory prevent complications by screening and early diagnosis, this approach is not rational if the diagnosed coeliac disease patients are not adequately treated (Wilson and Jungner 1968). In the future, it is evident that more studies from other countries with different availability of gluten-free products are needed.

12.3.2 Quality of life in asymptomatic patients

A diagnosis of coeliac disease and especially difficulties in maintaining a strict, life-long gluten-free diet are considered to have the greatest negative effect on patients who were found by screening and who therefore might conceivably have considered themselves asymptomatic and healthy before receiving their diagnosis. In Study **III**, screen-detected and clinically found children did not differ in their health-related quality of life, health concerns or experiences of daily life restrictions caused by the treatment after long-term follow-up in adulthood. This finding is in line with previous studies conducted in children, in which clinical presentation did not affect patients' experience of quality of life one to ten years after diagnosis (Fabiani et al. 2000, van Koppen et al. 2009, Kinos et al. 2012, Nordyke et al. 2013). However, it must be emphasized that in these earlier studies the patients were still children and their parents mainly responsible for their treatment.

All screen-detected patients might be considered asymptomatic, but on closer evaluation many of them actually suffer from unrecognized complaints. In Studies **II** and **III**, symptoms were detected in approximately half of the screen-detected patients. In previously published studies, symptoms were observed in 12-85% of risk-group children (Hansen et al. 2006, Kinos et al. 2012, Saadal et al. 2012, Tsouka et al. 2015, Agardh et al. 2015) and in 41-68% of mass-screened children (van Koppen et al. 2009, Al-Hussaini et al. 2017, Jansen et al. 2017). When comparing these varying results, it should be noted that the knowledge about coeliac disease diagnosis or abnormal laboratory results (Agardh et al. 2015) as well as the already initiated treatment (Ukkola et al. 2011, Kinos et al. 2012) may significantly affect how patients experience their symptoms. Therefore, the reported presence of symptoms may vary depending on the time of evaluation.

The presence of symptoms before diagnosis could play a more significant role than the diagnostic approach in the experience of later quality of life. In the present study, the subgroup of originally asymptomatic patients had more anxiety in adulthood than screened patients presenting with symptoms at diagnosis. However, the groups were otherwise comparable in different aspects of quality of life. Also, in an earlier Finnish study, quality of life had declined one year after the initiation of gluten-free diet in a few originally asymptomatic adult coeliac disease patients (Ukkola et al. 2011). In a recent Spanish study, better quality of life on a gluten-free diet was associated with classical clinical presentation at diagnosis, although the study included only three (0.7%) risk-group screened children (Torres et al. 2016).

Regarding asymptomatic patients, the important question is whether the benefits of coeliac disease diagnosis and treatment overcome possible harms. Apart from the risk of an unbalanced diet and the economic burden, a gluten-free diet may negatively affect everyday life. Therefore, the ease of the dietary treatment is essential, also from the aspect of quality of life (Casellas et al. 2008). Particularly asymptomatic patients may also fear eating gluten-containing products without noticing it if they have never experienced the symptoms associated with it. These aspects highlight the importance of appropriate education of patients about coeliac disease, its treatment and especially the low risk of dreaded long-term complications if a gluten-free diet is appropriately followed. Also, it should be remembered that asymptomatic patients should be supported by healthcare professionals: there is a risk that after the diagnosis they receive less attention from these professionals than those with severe symptoms and difficulties.

12.4 Strengths and limitations of the study

The major strength of the present study is the comprehensive data collected about the variable clinical, histological and laboratory parameters of coeliac disease diagnosis and the sociodemographic, health, quality of life and lifestyle factors after long-term follow-up in adulthood. Furthermore, nationwide and uniform criteria for coeliac disease diagnosis have been utilised during the entire study period in Finland.

The main limitation in all three studies (**I-III**) is the mostly their retrospective nature, when for example there was no structured questionnaire for the evaluation of symptoms at diagnosis. Due to the non-systematic collection of clinical characteristics and also laboratory results other than coeliac disease serology, especially before the 2000s, some of the data about diagnostic characteristics are

missing. However, it should be mentioned that data on most of the variables were available for over 80-90% of patients.

Study **I** covered almost the entire modern history of coeliac disease, and despite this long time period, diagnoses were made using the same protocols either by study authors or under their supervision. However, the earliest mucosal samples were obtained by Watson jejunal capsule, which may not be fully comparable to those taken later by gastroduodenoscopy. Furthermore, not all patients diagnosed especially before the twenty-first century could be included in Study **I**, and the present study was limited mainly to patients diagnosed in the catchment area of a single Tampere University Hospital.

The main strengths of Study **II** were the large cohort of children with accurate coeliac disease diagnoses: its limitations were its above-mentioned retrospective nature and some problematic aspects of the collection of some diagnostic data and the lack of a structured questionnaire for the evaluation of dietary adherence.

In Study **III**, the strengths were – in addition to reliable coeliac disease diagnoses – the opportunity to collect broad data about current characteristics of patients and the use of validated GRSR and PGWB testing, which have already been widely used with coeliac disease patients (Dimenäs et al. 1996, Revicki et al. 1998, Ukkola et al. 2011, Paarlahti et al. 2013, Mahadev et al. 2016). An obvious limitation was that only 42% of patients answered the study questionnaires. This is typical for postal surveys (Kalantar and Talley 1999) and predisposes to selection bias, usually towards too-positive results (Jacobsen and Thelle 1988, van Loon et al. 2003, Cheung et al. 2017). However, there were no significant differences between the responders and non-responders in most features, at least at the time of diagnosis. Another important aspect is that all adulthood follow-up data were self-reported. This is a clear limitation, for example in the evaluation of comorbidities, but the assessment of quality of life in coeliac disease should actually be self-reported, as it may differ significantly from the viewpoints of patient and doctor. Healthcare professionals often report too-positive evaluations (Vriezinga et al. 2017). Finally, the comparison of symptoms and quality of life between coeliac disease patients and non-coeliac controls could be affected by the older age and over-representation of women among the controls (Casellas et al. 2008, Lee et al. 2012).

13 SUMMARY AND CONCLUSIONS

Study **I** showed that there was a shift in paediatric coeliac disease towards a milder presentation, and that screening for risk groups increased over the course of 48 years in Finland. The most significant changes occurred at the turn of the twenty-first century. Thereafter, most of the changes seemed to reach a plateau, and the previously rising incidence of coeliac disease autoimmunity remained fluctuating without a clear trend. Similar changes and a possible plateau have also been reported in other autoimmune-type diseases (Berhan et al. 2011, Harjutsalo et al. 2013, Martín-de-Carpi et al. 2014, Henriksen et al. 2015), but this was the first time this was detected in coeliac disease. Some of these concurrent changes are explained by improved diagnostic methods and knowledge about the diseases, but it is likely that some as-yet unrecognized environmental factors also play a role here.

In Studies **II** and **III**, screen-detected patients were comparable to those found due to clinical suspicion regarding the severity of mucosal damage and coeliac antibody levels at diagnosis, which could indicate a similar risk of developing complications. Screen-detected patients suffered from anaemia and growth disturbances, but less often than clinically found patients did. Almost half of them also had previously unrecognized symptoms. The results were mainly similar in the subgroup of asymptomatic screen-detected patients. Furthermore, a median of 13 months after the diagnosis, strictness of dietary adherence in screen-detected patients was even better than in clinically found patients, and their clinical and serological response to the treatment was excellent.

After a median of 19 years from the diagnosis in adulthood in Study **III,** screen-detected children were still comparable to clinically detected patients in their dietary adherence and also in their overall experience of health, quality of life, presence of most comorbidities, and demographic and lifestyle characteristics. The diagnosis and treatment of childhood coeliac disease did not seem to affect more negatively those who were found in risk-group screening, except for the fact that originally asymptomatic patients had an elevated level of anxiety compared with symptomatic screened patients. However, also they were comparable with symptomatic patients in other aspects of quality of life.

Currently, without screening, most coeliac disease patients remain unrecognized, possibly with an increased risk of developing even severe and permanent complications such as infertility, fractures, refractory coeliac disease, and malignancies. The results of the present study support an active screening of children who belong to selected coeliac disease risk groups: mainly children with type 1 diabetes and family members of coeliac disease patients. However, especially originally asymptomatic patients should be given special attention due to an elevated risk of anxiety, even years after diagnosis.

Current evidence supports evaluating the possibility of coeliac disease in symptomatic patients and those who belong to selected risk groups (**Figure 6**). Future studies are needed to elucidate characteristics which could be used to identify coeliac disease patients with an increased risk of developing long-term complications without dietary treatment. One possibility might be the evaluation of different phenotypes of the disease, for example using advanced genetic methods (Hrdlickova et al. 2018). Currently, the decision about screening and therefore evaluation of possible coeliac disease relies strongly on the presence of symptoms (Chou et al. 2017). However, based on the present and previously published studies, symptoms are poor predictors of the histological severity of the disease (Brar et al. 2007, Jatla et al. 2009, Thomas et al. 2009). Especially the long-term prognosis and risk of complications in asymptomatic patients must be further clarified. Another future question is which diagnostic approach to coeliac disease would be the most appropriate. Patients are now identified most commonly through a combination of case-finding and risk-group screening (Rosén et al. 2014), although mass screening would probably be more effective. However, the issue is complicated and currently the evidence on the topic is scarce. Finally, our results regarding the changes in clinical features of paediatric coeliac disease could contribute to further studies identifying possible environmental factors that are affecting these changes, apart from incidence, also in clinical presentation.

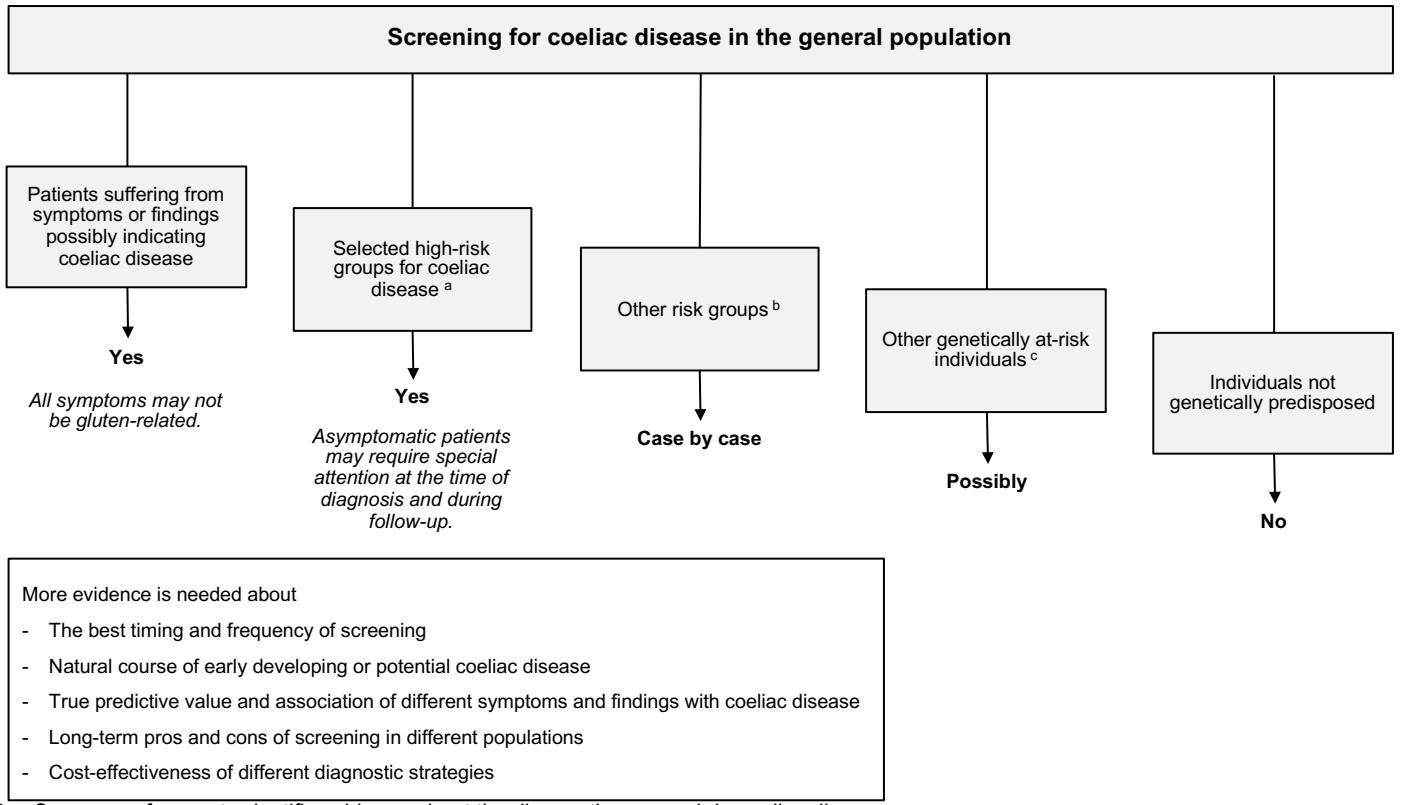

Figure 6. Summary of current scientific evidence about the diagnostic approach in coeliac disease.
[a] First-degree relatives of coeliac disease patients and children suffering from type 1 diabetes.
[b] Autoimmune thyroidal diseases, Down's syndrome, Turner's syndrome, autoimmune liver diseases, William's syndrome, Sjögren's syndrome, Addison's disease, selective IgA deficiency and IgA glomerulonephritis.
[c] HLA-DQ2 or HLA-DQ8.
HLA: human leucocyte antigen.

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APPENDIX 1: STUDY QUESTIONNAIRE

Tutkimusnumero_____

KYSELYKAAVAKE LAPSUUDESSA KELIAKIAAN SAIRASTUNEILLE, 5.5.2016

Rastita oikea vaihtoehto tai kirjoita vastauksesi tyhjille viivoille. Jos et halua tai osaa vastata johonkin kysymykseen, voit jättää sen tyhjäksi. Toivomme kuitenkin, että vastaisit kaikkiin osioihin.

Nimi_____ Syntymäaika _____

Puhelinnumero_____ Sähköposti _____

Olen työssä kokopäiväisesti ☐ osapäiväisesti ☐. Ammatti_____

En ole tällä hetkellä työssä ☐. Koulutus _____

Olen eläkkeellä ☐ vuodesta _____. Olen koululainen/opiskelija ☐ .

Jokin muu, mikä? _____

Olen ☐ En ole ☐ Keliakiayhdistyksen jäsen.

KELIAKIAAN SAIRASTUMINEN

1. Minä vuonna Sinulla todettiin keliakia? _____
2. Miksi Sinulla epäiltiin keliakiaa? _____
   _____
   _____
3. Tiedätkö, minkälainen vointisi oli ennen keliakiaan sairastumista? (voit valita monta)
   - ☐ Minulla oli suolisto-oireita
   - ☐ Minulla oli suoliston ulkopuolisia oireita
   - ☐ Olin oireeton
   - ☐ Keliakiaa epäiltiin sukulaisteni keliakian vuoksi
   - ☐ Keliakia löydettiin sattumalta muista syistä tehtyjen tutkimusten vuoksi
   - ☐ En tiedä

4. Tiedätkö, oliko Sinulla joitain seuraavista oireista tai vaivoista ennen keliakiadiagnoosin tekoa?

	Kyllä	Ei	En tiedä
4.1 Ripuli/löysät ulosteet	☐	☐	☐
4.2 Oksentelu	☐	☐	☐
4.3 Vatsakipu	☐	☐	☐
4.4 Ummetus	☐	☐	☐
4.5 Ilmavaivat	☐	☐	☐
4.6 Iho-oireita	☐	☐	☐
Jos kyllä, minkälaisia iho-oireita_____ _____			
4.7 Niveloireita	☐	☐	☐
4.8 Hampaiden kiillevaurioita	☐	☐	☐
4.9 Anemia (matala veren hemoglobiini)	☐	☐	☐
4.10 Kasvuongelmia	☐	☐	☐
Jos kyllä, pituuskasvun ☐ ja/vai painonkehityksen ☐ ongelmia			
4.11 Viivästynyt murrosikä	☐	☐	☐
4.12 Väsymystä	☐	☐	☐
4.13 Alakuloinen mieliala, mielialan vaihteluita, ahdistusta tms.	☐	☐	☐
4.14 Muita kuin edellä mainittuja oireita tai vaivoja	☐	☐	☐
Minkälaisia oireita? _____ _____ _____ _____			

VOINTISI NYKYÄÄN

5. Minkälaiseksi koet terveytesi nykyään?
   - ☐ erinomainen
   - ☐ hyvä
   - ☐ kohtalainen
   - ☐ huono

6. Oletko huolissasi omasta terveydestäsi?
   - ☐ en ollenkaan
   - ☐ vähän
   - ☐ jonkin verran
   - ☐ todella paljon

Miten kuvailisit tämän hetkistä vointiasi? _____
_____
_____

	Kyllä	Ei
7. Onko Sinulla ollut viime viikkojen aikana joitain oireita tai vaivoja, joiden ajattelet johtuvan keliakiasta?	☐	☐

Jos kyllä, minkälaisia oireita Sinulla on ollut? (esimerkiksi ripuli, vatsakivut, iho-oireet, niveloireet, väsymys, yms.) _____
_____
_____
_____

8. Mitkä ovat tämän hetkiset pituutesi _____ cm ja painosi _____ kg.

KELIAKIAN RUOKAVALIOHOIDON TOTEUTUMINEN

9. Oma näkemyksesi tämän hetkisestä gluteenittoman ruokavaliohoidon toteutumisesta
   - ☐ Noudatan gluteenitonta ruokavaliota hyvin tiukasti (lipsun äärimmäisen harvoin tai en koskaan)
   - ☐ Gluteeniton ruokavalioni lipsuu harvemmin kuin kerran kuukaudessa
   - ☐ Gluteeniton ruokavalioni lipsuu 1-5 kertaa kuukaudessa
   - ☐ Gluteeniton ruokavalioni lipsuu vähintään kerran viikossa
   - ☐ En noudata gluteenitonta ruokavaliohoitoa tällä hetkellä

	Kyllä	Ei
10. Onko keliakiadiagnoosin jälkeen ollut ajanjaksoja, jolloin gluteeniton ruokavaliohoito on jäänyt noudattamatta?	☐	☐
Jos kyllä, niin minä vuosina_____ ja kuinka kauan?_____		

	Kyllä	En
11. Jos et tällä hetkellä noudata gluteenitonta ruokavaliota, oletko joskus aiemmin noudattanut sitä?	☐	☐
Jos kyllä, niin minä vuosina_____ ja kuinka kauan?_____		

12. Jos et noudattanut gluteenitonta ruokavaliota, mikä oli syynä? _____
_____
_____

13. Miten koet gluteenittoman ruokavalion noudattamisen?
- ☐ Aina helppoa
- ☐ Yleensä helppoa
- ☐ Joskus helppoa, joskus vaikeaa
- ☐ Yleensä vaikeaa
- ☐ Aina vaikeaa

14. Mikä vaikuttaa siihen, että noudatat tiukkaa gluteenitonta ruokavaliota? (voit valita monta)
- ☐ Haluan välttää gluteenia sisältävien tuotteiden aiheuttamia oireita
- ☐ Haluan välttää gluteenin aiheuttamia pitkäkestoisia haittoja
- ☐ Gluteenittomien tuotteiden saatavuus
- ☐ Gluteenittomien tuotteiden hinta
- ☐ Jokin muu, mikä_____
_____

	Kyllä	En
15. Käytätkö ruokavaliossasi kauraa?	☐	☐

Jos kyllä, kuinka usein
- ☐ Päivittäin
- ☐ 2–3 kertaa viikossa
- ☐ Harvemmin

	Kyllä	En
16. Onko gluteeniton ruokavalio ja/tai keliakia rajoittanut elämääsi niin, että olet niiden takia joutunut jättämään jotain tekemättä?	☐	☐

Jos kyllä, mitä olet jättänyt tekemättä (voit valita monta)
- ☐ Ravintolassa syöminen
- ☐ Ulkomaille matkustaminen
- ☐ Kotimaassa matkustaminen
- ☐ Tuttavilla kyläily
- ☐ Jokin muu, mikä_____
_____

17. Kuinka usein keliakiaan liittyvää terveyttäsi seurataan (esim. laboratoriokokeet, lääkäri/hoitajakäynnit)?
- ☐ Ei koskaan
- ☐ Satunnaisesti
- ☐ 2–3 vuoden välein
- ☐ Kerran vuodessa
- ☐ Useammin

Jos keliakiaan liittyvää terveyttäsi seurataan, miten se toteutuu?
(voit valita monta)

☐ Käyn laboratoriokokeissa
☐ Käyn hoitajan vastaanotolla
☐ Käyn lääkärin vastaanotolla
☐ Muuten, miten? _____
_____

MUUT SAIRAUDET

18. Sairastatko joitain seuraavista lääkärin toteamista sairauksista?

	Kyllä	Ei
18.1 **Diabetes (eli sokeritauti)** tyypin 1 ☐ , tyypin 2 ☐ vai muu ☐ , mikä_____ vuodesta_____ lähtien ☐ tablettihoito ☐ insuliinihoito	☐	☐
18.2 **Kilpirauhassairaus** vuodesta_____ lähtien ☐ liikatoiminta ☐ vajaatoiminta	☐	☐
18.3 **Reumasairaus** vuodesta_____ lähtien Tarkempi diagnoosi_____	☐	☐
18.4 **Verenpainetauti** vuodesta_____ lähtien	☐	☐
18.5 **Sepelvaltimotauti** vuodesta_____ lähtien	☐	☐
18.6 **Aivohalvaus tai muu aivoverenkiertohäiriö** vuonna/vuosina_____	☐	☐
18.7 **Muu suolistosairaus kuin keliakia** (esim. Crohnin tauti, haavainen paksusuolen tulehdus, vatsahaava, tms.) vuodesta_____ lähtien tai milloin sairastit_____ Tarkempi diagnoosi_____	☐	☐
18.8 **Syöpäsairaus** vuodesta_____ lähtien tai milloin sairastit_____ Mikä/mitkä syövät? _____ _____	☐	☐

Kyllä Ei

18.9 **Osteoporoosi (eli luuston haurastuminen)** ☐ ☐

vuodesta_____ lähtien

Kyllä Ei

18.10 **Luun murtumia** ☐ ☐

Missä luissa ja minä vuosina?_____

_____

Mikä aiheutti murtumat? (esimerkiksi kaatuminen, auto-onnettomuus, tms.)

_____

_____

_____

Kyllä Ei

18.11 **Ihosairaus** ☐ ☐

vuodesta_____ lähtien tai milloin sairastit_____

Tarkempi diagnoosi_____

Kyllä Ei

18.12 **Syömishäiriö** ☐ ☐

vuodesta_____ lähtien tai milloin sairastit_____

Tarkempi diagnoosi_____

Kyllä Ei

18.13 **Masennus** ☐ ☐

vuodesta_____ lähtien tai milloin sairastit_____

Kyllä Ei

18.15 **Astma** ☐ ☐

vuodesta_____ lähtien tai milloin sairastit_____

Kyllä Ei

18.16 **Allergia** ☐ ☐

vuodesta_____ lähtien tai milloin sairastit_____

Mitä allergioita (esimerkiksi eläimet, ruoka-aineet, lääkeaineet, tms.)

_____

_____

Kyllä Ei

18.17 **Keskenmenoja** ☐ ☐

Minä vuosina _____

Kyllä Ei

18.18 **Jokin muu sairaus, mikä?** ☐ ☐

Diagnoosit ja sairastamisajat_____

_____

_____

_____

LÄÄKITYS

19. Käytän tällä hetkellä säännöllisesti seuraavia lääkärin määräämiä **lääkkeitä**:

_____
_____
_____

20. Käytän tällä hetkellä säännöllisesti seuraavia itsehoitol**ääkkeitä** (esim. särkylääkkeet, D-vitamiini, yms.):

_____
_____
_____

ELINTAVAT

	Kyllä	En
21. Tupakoitko nyt?	☐	☐

Jos kyllä, kuinka monta vuotta olet tupakoinut_____
Kuinka monta savuketta poltat päivässä (keskimäärin)_____

	Kyllä	En
22. Oletko aiemmin tupakoinut?	☐	☐

Jos kyllä, milloin lopetit? _____
Kuinka monta vuotta ehdit tupakoida? _____
Kuinka monta savuketta poltit päivässä (keskimäärin)_____

	Kyllä	En
23. Harrastatko säännöllisesti vapaa-ajan liikuntaa vähintään puoli tuntia kerralla niin, että ainakin lievästi hengästyt ja hikoilet?	☐	☐

Jos kyllä, kuinka usein

☐ päivittäin
☐ 4-6 kertaa viikossa
☐ 3 kertaa viikossa
☐ 1-2 kertaa viikossa
☐ harvemmin

LÄHISUKULAISET

24. Minulla on ☐ ei ole ☐ lapsia.

	Kyllä	Ei
25. Onko lähisukulaisillasi keliakiaa?	☐	☐

Jos on, ilmoita sukulaisuussuhde. Ilmoita myös, jos kyseessä on ihokeliakia.

_____
_____
_____
_____

KELIAKIAN SEULOMINEN

26. Keneltä keliakiaa pitäisi mielestäsi etsiä eli seuloa vasta-ainemittauksin?

☐ Ei keneltäkään
☐ Niiltä, ketkä hakeutuvat oireiden vuoksi lääkäriin
☐ Niiltä, kenellä tiedetään olevan kohonnut riski sairastua keliakiaan
(esimerkiksi tyypin 1 diabetesta sairastavat, keliakiapotilaiden lähisukulaiset)
☐ Kaikilta
☐ Joltain muulta, keneltä? _____

MAHDOLLISET JATKOTUTKIMUKSET

	Kyllä	Ei
27. Saako Sinuun ottaa yhteyttä mahdollisiin jatkotutkimuksiin (esim. henkilökohtainen haastattelu, keliakiavasta-aineiden määritys) liittyen?	☐	☐

Jos kyllä, miten toivoisit yhteydenottoa?

☐ Puhelimitse
☐ Sähköpostitse

Jos Sinulla on erityistä kysyttävää tai kommentoitavaa, voit kirjoittaa sen tähän.

_____
_____
_____

Kiitos vastauksestasi!

Lastentautien erikoislääkäri Kalle Kurppa ja lääketieteen lisensiaatti Laura Kivelä
Yhteydenotot: laura.kivela@fimnet.fi

Kyselylomakkeiden ja allekirjoitetun suostumuksen palautus oheisessa kuoressa Lasten terveyden tutkimuskeskukseen.

APPENDIX 2: PGWB QUESTIONNAIRE

R_____

PGWB INDEX

Nimi_____

Tutkimuksen tämä osa sisältää kysymyksiä siitä, miltä Teistä tuntuu ja kuinka Teillä on mennyt VIIMEKSI KULUNEEN VIIKON AIKANA. Jokaisen kysymyksen osalta rastittakaa (X) se vaihtoehto, joka parhaiten sopii Teidän kohdallenne.

1. Miltä Teistä on YLEISESTI ottaen TUNTUNUT viimeksi kuluneen viikon aikana?
   - ☐ Mielialani on ollut erinomainen
   - ☐ Mielialani on ollut oikein hyvä
   - ☐ Mielialani on ollut enimmäkseen hyvä
   - ☐ Mielialani on vaihdellut paljon
   - ☐ Mielialani on ollut enimmäkseen huono
   - ☐ Mielialani on ollut hyvin huono

2. Kuinka usein Teitä on VAIVANNUT JOKIN SAIRAUS, RUUMIILLINEN VAIVA, SÄRYT tai KIVUT viimeksi kuluneen viikon aikana?
   - ☐ Joka päivä
   - ☐ Melkein joka päivä
   - ☐ Noin puolet ajasta
   - ☐ Silloin tällöin, mutta vähemmän kuin puolet ajasta
   - ☐ Harvoin
   - ☐ Ei koskaan

R_____

3. Tunsitteko itsenne MASENTUNEEKSI viimeksi kuluneen viikon aikana?

   ☐ Kyllä – niin paljon, että minusta tuntui siltä, että ottaisin itseni hengiltä

   ☐ Kyllä – niin paljon, etten välittänyt mistään

   ☐ Kyllä – hyvin masentuneeksi melkein joka päivä

   ☐ Kyllä – melko masentuneeksi useita kertoja

   ☐ Kyllä – lievästi masentuneeksi silloin tällöin

   ☐ Ei – en ole kertaakaan tuntenut itseäni lainkaan masentuneeksi

4. Oletteko pystynyt HALLITSEMAAN KÄYTTÄYTYMISTÄNNE, AJATUKSIANNE, MIELIALOJANNE tai TUNTEITANNE viimeksi kuluneen viikon aikana?

   ☐ Kyllä, ehdottomasti

   ☐ Kyllä – useimmiten

   ☐ Yleensä

   ☐ En kovin hyvin

   ☐ En, ja se häiritsee minua jonkin verran

   ☐ En, ja se häiritsee minua kovasti

5. Onko Teitä vaivannut HERMOSTUNEISUUS tai LEVOTTOMUUS viimeksi kuluneen viikon aikana?

   ☐ Erittäin paljon, jopa niin, että en ole voinut tehdä työtä tai huolehtia asioista

   ☐ Hyvin paljon

   ☐ Melko paljon

   ☐ Jonkin verran, niin että se on vaivannut minua

   ☐ Vähän

   ☐ Ei lainkaan

6. Kuinka paljon TARMOA, PIRTEYTTÄ tai ELINVOIMAA Teillä on ollut viimeksi kuluneen viikon aikana?
   - ☐ Hyvin täynnä tarmoa – erittäin pirteä
   - ☐ Melko tarmokas suurimman osan ajasta
   - ☐ Tarmokkuuteni on vaihdellut melkoisesti
   - ☐ Yleensä vähän tarmoa tai pirteyttä
   - ☐ Hyvin vähän elinvoimaa tai tarmoa suurimman osan ajasta
   - ☐ Ei lainkaan tarmoa tai elinvoimaa – olen tuntenut itseni loppuun ajetuksi tai loppuun kuluneeksi

7. Olen tuntenut itseni ALAKULOISEKSI JA SYNKKÄMIELISEKSI viimeksi kuluneen viikon aikana?
   - ☐ En kertaakaan
   - ☐ Vähän tänä aikana
   - ☐ Jonkin verran tänä aikana
   - ☐ Melkoisen osan tästä ajasta
   - ☐ Suurimman osan tästä ajasta
   - ☐ Koko ajan

8. Oletteko yleisesti ollut KIREÄ tai tuntenut itsenne JÄNNITTYNEEKSI viimeksi kuluneen viikon aikana?
   - ☐ Kyllä, erittäin jännittyneeksi suurimman osan ajasta tai koko ajan
   - ☐ Kyllä, hyvin jännittyneeksi suurimman osan ajasta
   - ☐ En ole ollut koko ajan kireä, mutta olen tuntenut itseni melko jännittyneeksi useita kertoja
   - ☐ Olen tuntenut itseni vähän jännittyneeksi muutamia kertoja
   - ☐ En ole yleensä tuntenut itseäni jännittyneeksi
   - ☐ En ole lainkaan tuntenut itseäni jännittyneeksi

9. Kuinka ONNELLINEN, TYYTYVÄINEN tai MIELISSÄNNE olette ollut viimeksi kuluneen viikon aikana?
   - ☐ Erittäin onnellinen, en olisi voinut olla tyytyväisempi tai enemmän mielissäni
   - ☐ Hyvin onnellinen suurimman osan ajasta
   - ☐ Yleensä tyytyväinen ja mielissäni
   - ☐ Joskus melko onnellinen ja joskus melko onneton
   - ☐ Yleensä tyytymätön ja onneton
   - ☐ Hyvin tyytymätön tai onneton suurimman osan ajasta tai koko ajan

10. Oletteko tuntenut itsenne riittävän TERVEEKSI tekemään asioita, joita haluatte tehdä tai Teidän on ollut pakko tehdä viimeksi kuluneen viikon aikana?
   - ☐ Kyllä, ehdottomasti
   - ☐ Suurimman osan ajasta
   - ☐ Terveysongelmat ovat merkittävästi rajoittaneet minua
   - ☐ Olen ollut vain niin terve, että olen voinut huolehtia itsestäni
   - ☐ Olen tarvinnut jonkin verran apua itseni huolehtimisessa
   - ☐ Olen tarvinnut toista henkilöä auttamaan itseäni useimmissa tai kaikissa asioissa, joita minun on täytynyt tehdä

11. Oletteko tuntenut itsenne niin SURULLISEKSI, LANNISTUNEEKSI tai TOIVOTTOMAKSI, että olette miettinyt, onko millään mitään merkitystä viimeksi kuluneen viikon aikana?
   - ☐ Erittäin paljon – niin paljon, että olen ollut valmis luovuttamaan
   - ☐ Hyvin paljon
   - ☐ Melko lailla
   - ☐ Jonkin verran – sen verran, että se on vaivannut minua
   - ☐ Vähän
   - ☐ En lainkaan

12. Oletteko herännyt PIRTEÄNÄ ja LEVÄNNEENÄ viimeksi kuluneen viikon aikana?

- ☐ En kertaakaan
- ☐ Muutaman harvan kerran
- ☐ Joitakin kertoja
- ☐ Aika monta kertaa
- ☐ Useimmiten
- ☐ Joka kerta

13. Oletteko ollut HUOLISSANNE tai LEVOTON TERVEYDESTÄNNE viimeksi kuluneen viikon aikana?

- ☐ Erittäin paljon
- ☐ Hyvin paljon
- ☐ Melko paljon
- ☐ Jonkin verran, mutta en kovin paljon
- ☐ Käytännöllisesti katsoen en koskaan
- ☐ En lainkaan

14. Onko Teistä tuntunut siltä, että olisitte ”MENETTÄMÄSSÄ JÄRKENNE” tai KONTROLLINNE siitä, miten TOIMITTE, PUHUTTE, AJATTELETTE, TUNNETTE tai MITÄ MUISTATTE viimeksi kuluneen viikon aikana?

- ☐ Ei lainkaan
- ☐ Vain vähän
- ☐ Jonkin verran, mutta ei niin paljon, että olisin ollut huolissani tai levoton siitä
- ☐ Jonkin verran ja olen ollut vähän huolissani
- ☐ Jonkin verran ja olen ollut melko huolissani
- ☐ Kyllä, hyvin paljon ja olen ollut hyvin huolissani

15. Päivittäinen elämäni on ollut TÄYNNÄ minua KIINNOSTAVIA ASIOITA viimeksi kuluneen viikon aikana?

☐ Ei lainkaan tänä aikana

☐ Vain pienen osan tästä ajasta

☐ Joskus

☐ Melkoisen osan tästä ajasta

☐ Suurimman osan tästä ajasta

☐ Koko ajan

16. Oletteko tuntenut itsenne AKTIIVISEKSI/TARMOKKAAKSI tai TYLSÄKSI/VELTOKSI viimeksi kuluneen viikon aikana?

☐ Hyvin aktiiviseksi/tarmokkaaksi joka päivä

☐ Enimmäkseen aktiiviseksi/tarmokkaaksi – en koskaan tylsäksi/veltoksi

☐ Melko aktiiviseksi/tarmokkaaksi – harvoin tylsäksi/veltoksi

☐ Melko tylsäksi/veltoksi – harvoin aktiiviseksi/tarmokkaaksi

☐ Enimmäkseen tylsäksi/veltoksi – en koskaan aktiiviseksi/tarmokkaaksi

☐ Hyvin tylsäksi/veltoksi joka päivä

17. Oletteko ollut HUOLESTUNUT, HARMISSANNE tai AHDISTUNUT viimeksi kuluneen viikon aikana?

☐ Erittäin paljon – niin paljon, että olen tuntenut itseni melkein sairaaksi huolestuneisuudesta

☐ Hyvin paljon

☐ Melko lailla

☐ Jonkin verran – sen verran, että se on vaivannut minua

☐ Vähän

☐ En lainkaan

18. Olen tuntenut itseni TASAPAINOISEKSI ja VARMAKSI viimeksi kuluneen viikon aikana?

- ☐ En lainkaan tänä aikana
- ☐ Pienen osan tästä ajasta
- ☐ Joskus
- ☐ Huomattavan osan tästä ajasta
- ☐ Suurimman osan tästä ajasta
- ☐ Koko ajan

19. Oletteko tuntenut itsenne LEVOLLISEKSI/HUOJENTUNEEKSI vai PINGOTTUNEEKSI/KIREÄKSI viimeksi kuluneen viikon aikana?

- ☐ Olen tuntenut itseni levolliseksi ja huojentuneeksi koko viikon
- ☐ Olen tuntenut itseni levolliseksi ja huojentuneeksi suurimman osan ajasta
- ☐ Yleensä olen tuntenut itseni levolliseksi, mutta ajoittain olen tuntenut itseni melko pingottuneeksi
- ☐ Yleensä olen tuntenut itseni pingottuneeksi, mutta ajoittain olen tuntenut itseni melko levolliseksi
- ☐ Olen tuntenut itseni pingottuneeksi/kireäksi suurimman osan ajasta
- ☐ Olen tuntenut itseni hyvin pingottuneeksi/kireäksi koko ajan

20. Olen tuntenut itseni ILOISEKSI/HUOLETTOMAKSI viimeksi kuluneen viikon aikana?

- ☐ En lainkaan tänä aikana
- ☐ Pienen osan tästä ajasta
- ☐ Joskus
- ☐ Melkoisen osan tästä ajasta
- ☐ Suurimman osan tästä ajasta
- ☐ Koko ajan

R_____

21. Olen tuntenut itseni VÄSYNEEKSI ja LOPPUUN KULUNEEKSI viimeksi kuluneen viikon aikana?

☐ En lainkaan tänä aikana

☐ Pienen osan tästä ajasta

☐ Joskus

☐ Melkoisen osan tästä ajasta

☐ Suurimman osan tästä ajasta

☐ Koko ajan

22. Oletteko tuntenut itsenne ”STRESSAANTUNEEKSI”, RASITTUNEEKSI tai PAINEEN ALAISEKSI viimeksi kuluneen viikon aikana?

☐ Kyllä, melkein enemmän kuin voin sietää tai kestää

☐ Kyllä melko lailla

☐ Kyllä, jonkin verran – enemmän kuin tavallisesti

☐ Kyllä, jonkin verran – kuten tavallisesti

☐ Kyllä, vähän

☐ En lainkaan

TARKISTAKAA, ETTÄ OLETTE VASTANNUT KAIKKIIN KYSYMYKSIIN!

KIITOS HYVÄSTÄ YHTEISTYÖSTÄ.

APPENDIX 3: GSRS QUESTIONNAIRE

R_____

THE GASTROINTESTINAL SYMPTOM RATING SCALE

(GSRS)

Nimi_____

Lue tämä ensin:

Tutkimus sisältää kysymyksiä voinnistasi ja tilastasi kuluneen viikon aikana. Merkitse rastilla (X) se vaihtoehto, joka sopii parhaiten sinuun ja tilaasi.

1. Onko Sinulla ollut VATSAKIPUJA kuluneen viikon aikana? (Vatsakivuilla tarkoitetaan kaikenlaista kipua tai särkyä vatsassa.)
   - ☐ Ei minkäänlaisia vaivoja
   - ☐ Vähäpätöisiä vaivoja
   - ☐ Lieviä vaivoja
   - ☐ Kohtalaisia vaivoja
   - ☐ Melko pahoja vaivoja
   - ☐ Pahoja vaivoja
   - ☐ Erittäin pahoja vaivoja

2. Onko Sinulla ollut NÄRÄSTYSTÄ kuluneen viikon aikana? (Närästyksellä tarkoitetaan kirvelevää tai polttavaa pahanolontunnetta rintalastan takana.)
   - ☐ Ei minkäänlaisia vaivoja
   - ☐ Vähäpätöisiä vaivoja
   - ☐ Lieviä vaivoja
   - ☐ Kohtalaisia vaivoja
   - ☐ Melko pahoja vaivoja
   - ☐ Pahoja vaivoja
   - ☐ Erittäin pahoja vaivoja

3. Onko Sinulla ollut HAPPAMIA RÖYHTÄISYJÄ kuluneen viikon aikana? (Happamilla röyhtäisyillä tarkoitetaan äkillisiä, hapanta vatsanestettä sisältäviä röyhtäisyjä.)
   - ☐ Ei minkäänlaisia vaivoja
   - ☐ Vähäpätöisiä vaivoja
   - ☐ Lieviä vaivoja
   - ☐ Kohtalaisia vaivoja
   - ☐ Melko pahoja vaivoja
   - ☐ Pahoja vaivoja
   - ☐ Erittäin pahoja vaivoja

4. Onko Sinua HIUKAISSUT kuluneen viikon aikana? (Hiukaisulla tarkoitetaan vatsassa olevaa hiukovaa tunnetta, johon liittyy tarve syödä aterioiden välillä.)
   - ☐ Ei minkäänlaisia vaivoja
   - ☐ Vähäpätöisiä vaivoja
   - ☐ Lieviä vaivoja
   - ☐ Kohtalaisia vaivoja
   - ☐ Melko pahoja vaivoja
   - ☐ Pahoja vaivoja
   - ☐ Erittäin pahoja vaivoja

5. Onko Sinulla ollut PAHOINVOINTIA kuluneen viikon aikana? (Pahoinvoinnilla tarkoitetaan pahanolontunnetta, joka saattaa muuttua kuvotukseksi tai oksentamiseksi.)
   - ☐ Ei minkäänlaisia vaivoja
   - ☐ Vähäpätöisiä vaivoja
   - ☐ Lieviä vaivoja
   - ☐ Kohtalaisia vaivoja
   - ☐ Melko pahoja vaivoja
   - ☐ Pahoja vaivoja
   - ☐ Erittäin pahoja vaivoja

6. Onko vatsasi KURISSUT kuluneen viikon aikana? (Kurinalla tarkoitetaan vatsassa tuntuvaa värinää tai ”murinaa”.)
   - ☐ Ei minkäänlaisia vaivoja
   - ☐ Vähäpätöisiä vaivoja
   - ☐ Lieviä vaivoja
   - ☐ Kohtalaisia vaivoja
   - ☐ Melko pahoja vaivoja
   - ☐ Pahoja vaivoja
   - ☐ Erittäin pahoja vaivoja

7. Onko vatsaasi TURVOTTANUT kuluneen viikon aikana? (Turvotuksella tarkoitetaan vatsassa tuntuvaa pingotusta, johon usein liittyy tuntemuksia ilmavaivoista.)
   - ☐ Ei minkäänlaisia vaivoja
   - ☐ Vähäpätöisiä vaivoja
   - ☐ Lieviä vaivoja
   - ☐ Kohtalaisia vaivoja
   - ☐ Melko pahoja vaivoja
   - ☐ Pahoja vaivoja
   - ☐ Erittäin pahoja vaivoja

8. Onko Sinua vaivannut RÖYHTÄILY kuluneen viikon aikana? (Röyhtäilyllä tarkoitetaan tarvetta päästää ilmaa suun kautta, minkä yhteydessä vatsassa tuntuva pingotus usein helpottuu.)
   - ☐ Ei minkäänlaisia vaivoja
   - ☐ Vähäpätöisiä vaivoja
   - ☐ Lieviä vaivoja
   - ☐ Kohtalaisia vaivoja
   - ☐ Melko pahoja vaivoja
   - ☐ Pahoja vaivoja
   - ☐ Erittäin pahoja vaivoja

9. Onko Sinulla ollut ILMAVAIVOJA kuluneen viikon aikana? (Ilmavaivoilla tarkoitetaan tässä tarvetta päästää ilmaa, jonka yhteydessä vatsassa tuntuva pingotus usein helpottuu.)
   - ☐ Ei minkäänlaisia vaivoja
   - ☐ Vähäpätöisiä vaivoja
   - ☐ Lieviä vaivoja
   - ☐ Kohtalaisia vaivoja
   - ☐ Melko pahoja vaivoja
   - ☐ Pahoja vaivoja
   - ☐ Erittäin pahoja vaivoja

10. Onko Sinua vaivannut UMMETUS kuluneen viikon aikana? (Ummetuksella tarkoitetaan ulostuskertojen harventumista.)
   - ☐ Ei minkäänlaisia vaivoja
   - ☐ Vähäpätöisiä vaivoja
   - ☐ Lieviä vaivoja
   - ☐ Kohtalaisia vaivoja
   - ☐ Melko pahoja vaivoja
   - ☐ Pahoja vaivoja
   - ☐ Erittäin pahoja vaivoja

11. Onko Sinua vaivannut RIPULI kuluneen viikon aikana? (Ripulilla tarkoitetaan ulostuskertojen lisääntymistä.)
   - ☐ Ei minkäänlaisia vaivoja
   - ☐ Vähäpätöisiä vaivoja
   - ☐ Lieviä vaivoja
   - ☐ Kohtalaisia vaivoja
   - ☐ Melko pahoja vaivoja
   - ☐ Pahoja vaivoja
   - ☐ Erittäin pahoja vaivoja

12. Onko Sinua vaivannut LÖYSÄ VATSA kuluneen viikon aikana? (Jos ulosteesi on välillä ollut kovaa ja välillä löysää, ilmoita vain, missä määrin ulosteesi löysyys on Sinua vaivannut.)
    - ☐ Ei minkäänlaisia vaivoja
    - ☐ Vähäpätöisiä vaivoja
    - ☐ Lieviä vaivoja
    - ☐ Kohtalaisia vaivoja
    - ☐ Melko pahoja vaivoja
    - ☐ Pahoja vaivoja
    - ☐ Erittäin pahoja vaivoja

13. Onko Sinua vaivannut KOVA VATSA kuluneen viikon aikana? (Jos ulosteesi on välillä ollut kovaa ja välillä löysää, ilmoita vain, missä määrin ulosteesi kovuus on Sinua vaivannut.)
    - ☐ Ei minkäänlaisia vaivoja
    - ☐ Vähäpätöisiä vaivoja
    - ☐ Lieviä vaivoja
    - ☐ Kohtalaisia vaivoja
    - ☐ Melko pahoja vaivoja
    - ☐ Pahoja vaivoja
    - ☐ Erittäin pahoja vaivoja

14. Onko Sinua vaivannut kuluneen viikon aikana PAKOTTAVA ULOSTAMISEN TARVE? (Pakottavalla ulostamisen tarpeella tarkoitetaan äkillistä tarvetta käydä WC:ssä. Siihen liittyy usein puutteellisen pidättämiskyvyn tunne.)
    - ☐ Ei minkäänlaisia vaivoja
    - ☐ Vähäpätöisiä vaivoja
    - ☐ Lieviä vaivoja
    - ☐ Kohtalaisia vaivoja
    - ☐ Melko pahoja vaivoja
    - ☐ Pahoja vaivoja
    - ☐ Erittäin pahoja vaivoja

15. Onko Sinulla kuluneen viikon aikana ollut ULOSTAMISEN YHTEYDESSÄ TUNNE, ETTÄ SUOLI EI OLE TYHJENTYNYT KOKONAAN? (Tällä tarkoitetaan, että suoli ei ponnistuksista huolimatta tunnu tyhjentyneen kunnolla.)

☐ Ei minkäänlaisia vaivoja

☐ Vähäpätöisiä vaivoja

☐ Lieviä vaivoja

☐ Kohtalaisia vaivoja

☐ Melko pahoja vaivoja

☐ Pahoja vaivoja

☐ Erittäin pahoja vaivoja

16. ONKO SINULLA VIIMEISEN KUUKAUDEN AIKANA ESIINTYNYT SEURAAVIA OIREITA (rengasta sopivat vaihtoehdot)

a. kielikipuja
b. haavaumia suussa
c. luustokipuja
d. puutumista
e. muuta, mitä _____

TARKISTA, ETTÄ OLET VASTANNUT KAIKKIIN KYSYMYKSIIN, ENNEN KUIN PALAUTAT LOMAKKEEN.

KIITOS AVUSTASI!

ORIGINAL PUBLICATIONS

Presentation of Celiac Disease in Finnish Children Is No Longer Changing: A 50-Year Perspective

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Objectives To chart trends in the presentation of celiac disease in a large cohort of Finnish children diagnosed over a period of 48 years.

Study design Clinical and serologic data, severity of small-bowel mucosal damage, and presence of associated conditions were gathered from 596 children diagnosed with celiac disease in 1966-2013. The children were divided into 4 groups based on the year of diagnosis (before 1980, 1980-1999, 2000-2009, and 2010-2013), and the variables were compared between the periods. The incidence of celiac disease autoimmunity in 2001-2013 was calculated based on the number of new antibody-positive cases in each year.

Results Age at diagnosis rose from median 4.3 years before 1980 to between 7.6 and 9.0 years in the later periods. The severity of clinical presentation, in general, became milder and poor growth less common during the entire study period of 50 years. Percentages of children with classical gastrointestinal presentation decreased, and those with atypical or subclinical presentation increased after the 1990s, these changes leveling off in 2000-2013. Similarly, the severity of small-bowel mucosal damage was milder after the 1990s. The incidence of celiac disease autoimmunity increased in the early 2000s but then fluctuated without a clear trend. There were no significant secular changes in sex distribution, presence of anemia, levels of celiac antibodies, or celiac disease-associated conditions.

Conclusions The clinical and histologic presentation of celiac disease in children became milder, especially in the 1980s and 1990s. However, most of these changes have reached a plateau in recent years. *(J Pediatr 2015;167:1109-15)*.

Celiac disease is a chronic condition in which an immunoreaction to gluten causes small-bowel mucosal damage and various symptoms in susceptible individuals.[1] During the past few decades, the incidence of the disease has increased significantly,[2-5] constituting a major health problem affecting up to 1%-3% of children.[6,7] Concomitant with the increasing incidence, changes in the clinical presentation have been observed since the 1980s.[8] Instead of the classical symptoms of diarrhea and failure to thrive, atypical symptoms have been increasingly encountered, as well as asymptomatic patients detected by targeted screening of at-risk groups.[2,3,9-12] In addition, the average age at diagnosis has risen from <2 years[8] up to 6-9 years in many developed countries.[2,3,9,11-14] Most of these changes are probably explained by new serologic tools,[2,9] increased awareness among physicians, and at-risk group screenings.[10] This notwithstanding, there are differences in the prevalence and presentation of celiac disease between closely located geographic areas and fluctuations even within the same country,[15,16] and the true prevalence of the disease has also increased.[3,17,18] These observations suggest that environmental factors have a role in these phenomena. Related changes have also been observed in other autoimmune diseases.[19-21] However, at least in some developed countries, these changes might already have reached a plateau.[22-24] Thus far, no similar trends in celiac disease has been reported.

In Finland, celiac disease is particularly common[6] and centralized diagnostics, together with nationwide guidelines, enable reliable long-term evaluation of the natural history of the disease. We sought to characterize trends in the clinical and histologic presentation and incidence of celiac disease in a large and unique cohort of children diagnosed over a period of almost 50 years.

CDA	Celiac disease autoimmunity
EmA	Endomysial antibody
PVA	Partial villous atrophy
SVA	Subtotal villous atrophy
TG2ab	Transglutaminase 2 antibody
TVA	Total villous atrophy

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Methods

The study was conducted in the Tampere Center for Child Health Research, University of Tampere and Tampere University Hospital. Inclusion criteria were confirmed celiac disease and age under 18 years at diagnosis. The patients were collected from our continuously updated research database comprising information on children diagnosed with celiac disease from 1966 to the present. A considerable proportion of the information in our database has been collected prospectively. Apart from this, data were collected from the medical records and, when these proved inadequate, supplemented with personal interviews by a study nurse with expertise in celiac disease. Collection of medical records and patient interviews was approved by the Pediatric Clinic of Tampere University Hospital and the Ethics Committee of the Pirkanmaa Hospital District, Tampere, Finland. All subjects and/or their parents gave written informed consent to participate in the supplementary personal interviews.

In Finland, the diagnostics of celiac disease in children is coordinated by the university hospitals (currently 5), and nationwide guidelines are systematically applied in all these tertiary centers.[25] All patients with celiac disease receive financial compensation from the government, a definitive biopsy-proven diagnosis being required. In our database, early diagnoses before the 1970s were made almost exclusively at the pediatric department in Helsinki University Hospital, and most of the later diagnoses in Tampere University Hospital. A great majority of the database diagnoses from the 1960s to the present were made either personally or under the supervision of the study authors.

Altogether 596 children with celiac disease fulfilled the inclusion criteria and comprised the study population. To analyze the clinical incidence of celiac disease from the year 2001 onward, the annual number of seropositive children referred to our hospital for gastrointestinal endoscopy because of celiac disease suspicion in 2001-2013 was calculated (see below).

The following data at the time of celiac disease diagnosis were collected on all children: age, sex, clinical presentation, presence of growth failure or overweight, presence of anemia and hemoglobin value, severity of the small-bowel mucosal damage, serum celiac disease-specific antibodies, and presence of celiac disease-associated conditions, including type 1 diabetes, autoimmune thyroidal disease, and Down syndrome.

The 596 study children were divided into 3 subgroups based on their age at celiac disease diagnosis as follows: (1) infants (<2 years of age); (2) toddlers/preschoolers (2-7 years of age); and (3) school-aged children (>7 years of age). The clinical presentation of the disease was subcategorized into 3 groups according to the main symptoms recorded at diagnosis: (1) gastrointestinal symptoms including diarrhea, vomiting, abdominal pain, and constipation; (2) extra-intestinal symptoms such as arthralgia, dental enamel defects, neurologic and musculoskeletal symptoms, short stature or failure to thrive, and elevated liver enzymes; and (3) children detected by screening in at-risk groups (eg, family history of celiac disease or presence of an associated disorder such as type 1 diabetes). The severity of clinical presentation at diagnosis was classified into 4 grades as follows: (1) no clinical symptoms (screen-detected asymptomatic subjects); (2) mild symptoms (occasionally disturbing gastrointestinal or extra-intestinal symptoms and normal growth); (3) moderate symptoms (symptoms more distracting or frequent or a combination of several symptoms); and (4) severe symptoms (symptoms seriously disturbing daily life, eg, recurrent nighttime awakenings because of pain or symptoms requiring acute inpatient care).

Poor growth was defined as a significant height or weight deceleration compared with the reference rate for age and sex or compared with expected height based on midparental height. This method has long been used in our clinical practice and has been proven to be a sensitive method to detect growth failure in untreated celiac disease.[26] Height-to-weight ratio was used to define if a child was overweight. It describes a percentual difference of child's weight compared with the median weight of those with same height. Children were considered to be overweight when the height-to-weight ratio was >10% (<7 years old) or >20% (≥7 years old) on nationally standardized growth charts.[27] Anemia at diagnosis was defined as a hemoglobin value (g/L) below the age- and sex-matched reference value.

Small-bowel mucosal biopsies before 1986 were obtained either using the Watson gastrointestinal biopsy capsule or during upper gastrointestinal endoscopy; from 1986 onward, endoscopy has been used exclusively. The degree of small-bowel mucosal damage was categorized into partial (PVA), subtotal (SVA), and total villous atrophy (TVA) because this grading has been systematically applied by pathologists during the entire study period. The corresponding Marsh-Oberhuber grades are approximately IIIa, IIIb, and IIIc.[28]

From the 1970s to the 1990s, anti-gliadin and antireticulin antibodies were used in most cases. Human umbilical cord-based measurement of endomysial antibodies (EmAs) was introduced in 1994, and serum transglutaminase 2 antibody (TG2ab) in 1997; assays for these have been used as a first-line screening method for celiac disease in our clinical practice since the end of the 1990s.[29] As a result, the median values for EmA in 2000-2009 and 2010-2013 could be calculated. This could not be done with TG2ab because the testing methods have varied over time, and the cut-off values for positivity have been set by manufacturers using different criteria.[30]

From the year 2001 onward, practically all children referred to our hospital because of celiac disease suspicion have been EmA- and/or TG2ab-positive. We defined celiac disease autoimmunity (CDA) as elevated TG2ab/EmA regardless of biopsy results,[31] and subsequently estimated the annual incidence rate of CDA in 2001-2013 by dividing the number of seropositive cases by the number of at-risk children in our catchment area (119 243-121 581 during the

corresponding period).[32] In our previous study, celiac disease was confirmed by biopsy in 80.5% of seropositive children, indicating that CDA overestimates the incidence of biopsy-proven celiac disease by approximately 10%-20%.[6] On the other hand, it is more objective and not prone to different sampling techniques or subjective interpretations by the pathologist.

Finally, the year of celiac disease diagnosis was defined according to the date of the first confirmatory small-bowel mucosal biopsy, and the study data were compared among 4 different periods: celiac disease diagnosis: (1) before 1980; (2) 1980-1999; (3) 2000-2009; and (4) 2010-2013. These periods were selected to reveal possible changes in the clinical presentation of celiac disease after the major diagnostic improvements and especially during the 21st century.

Statistical Analyses

Categorical variables are reported as percentage distributions and numeric variables as medians with quartiles. To detect differences in categorical variables χ^2 test or Fisher exact test was used, and to compare numeric variables Kruskal-Wallis or Mann-Whitney U test. The annual incidence rate of CDA is reported as cases/100 000/y and trends in it as incidence rate ratios with 95% CIs calculated by applying Poisson regression. A P value of <.05 was considered significant. Statistical analyses were performed with SPSS v 22 (IBM Corporation, Armonk, New York) and Stata version 13 (StataCorp LP, College Station, Texas).

Results

Clinical features in the 596 study children during the different periods are presented in Table I. The age at celiac disease diagnosis was significantly lower before 1980 compared with the later periods. Poor growth was common before 1980s but became less common in 1980-2009, decreasing further in 2010-2013. The proportion of overweight children did not differ significantly between 2000-2009 and 2010-2013; there were insufficient data from the previous era. Anemia was less common, and the median hemoglobin value higher in 2000-2009, but otherwise there was no significant difference in these between the time-points. There were some fluctuations in the sex distribution and celiac disease-associated comorbidities, but these were not significant. The median values for EmA remained at the same level in 2000-2013 (Table I).

Concurrent with increasing age, the proportion of affected infants decreased significantly after the 1970s; simultaneously the percentage of preschoolers increased and that of older children fluctuated without systematic trend (Figure 1, A). The number of screen-detected patients increased from the below 5% seen in the early periods to the 31% and 26% found in 2000-2009 and 2010-2013, respectively. Simultaneously, the proportion (but not the total number) of children with gastrointestinal and extra-intestinal symptoms decreased (Figure 1, B). The severity of clinical presentation became milder during the study period, and especially the percentage of asymptomatic patients increased after the 1990s, but remaining almost unchanged in 2000-2013 (Figure 1, C). Likewise, the degree of small-bowel mucosal villous atrophy became milder after the 1990s, as the percentage of subjects with TVA decreased substantially whereas that of PVA nearly tripled; this change reached a plateau in 2000-2013 (Figure 1, D).

Altogether 49% (n = 292) of the children involved suffered from gastrointestinal complaints as the main presentation at diagnosis (Table II). The patients with gastrointestinal presentation were younger than all 596 study patients together in each period except before 1980. A major change among gastrointestinal symptoms occurred at the turn of the 21st century, when the proportion of children with diarrhea and vomiting decreased markedly and simultaneously abdominal pain and constipation increased. The increase in these latter complaints continued in 2010-2013 (Table II). Besides the changes in type, the severity of the clinical presentation became milder. In addition, as in study patients, in general, the severity of the mucosal damage abated in children with gastrointestinal presentation in 2000-2010, the changes subsequently leveling off (Table III). Similar

Table I. Clinical characteristics at the time of celiac disease diagnosis and presence of associated comorbidities in 596 children with celiac disease divided into 4 periods based on year of diagnosis

	<1980, n = 46	1980-1999, n = 69	2000-2009, n = 318	2010-2013, n = 163	*P* value*
Age, median (Q_1, Q_3), y	4.3 (1.2, 10.6)	9.0 (3.0, 14.4)	8.0 (5.0, 11.9)	7.6 (4.3, 11.7)	.008
Females, %	67	59	61	71	.125
Poor growth, %	66	36	34	23	<.001
Overweight or obese, %	ND	ND	10†	14‡	.305
Anemia, %	23	23	14	26	.014
Hb, median (Q_1, Q_3), g/L	122 (115, 130)	125 (110, 132)§	127 (119, 133)¶	122 (110, 130)**	.007
Comorbidities, %					
Type 1 diabetes	2	10	8	9	.455
Thyroidal disease	7	4	2	1	.076
Down syndrome	2	3	1	1	.394
EmA, median (Q_1, Q_3), titer	ND	ND	1:500†† (1:100, 1:1000)	1:500‡‡ (1:100, 1:1250)	.860

Hb, hemoglobin; *ND*, no or insufficient data; Q_1, lower quartile; Q_3, upper quartile.
Data were available in >80% of cases in each variable except in (n): †133, ‡99, §54, ¶175, **120, ††191, ‡‡126.
**P* value denotes statistical difference among the 4 periods.

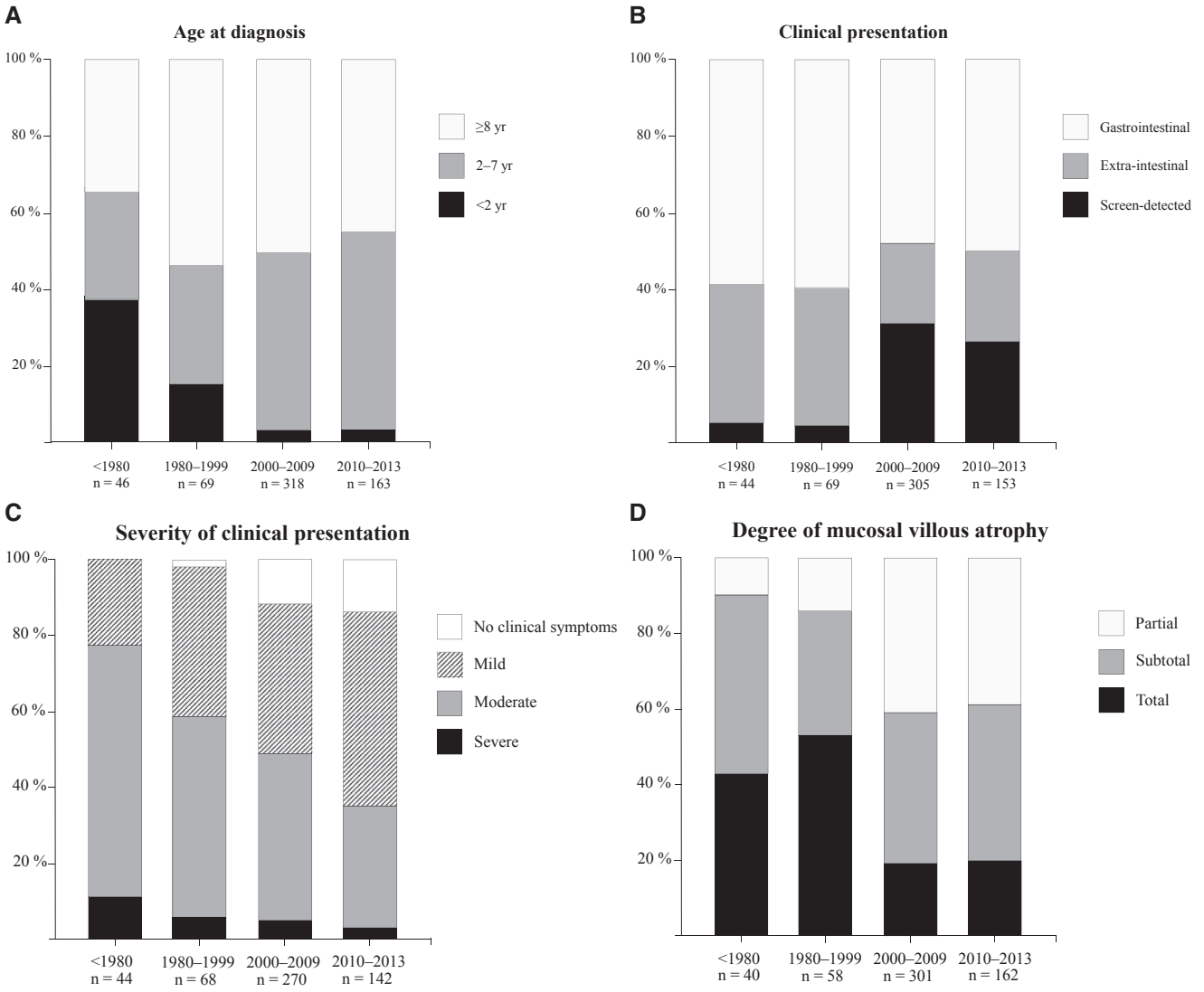

Figure 1. **A,** Age, **B,** clinical presentation, **C,** severity of clinical presentation, and **D,** degree of small-bowel mucosal villous atrophy at diagnosis in 596 children with celiac disease divided into different time periods.

trends in the severity of clinical presentation and histology were seen when children presenting with diarrhea were evaluated separately (data not shown). In a subgroup analysis among children with moderate or severe gastrointestinal presentation, the presence of PVA increased from 5%-17% before the 2000s to 43%-46% in 2000-2013; at the same time TVA decreased from 61%-62% to 18%-22% (P = .001).

In a subgroup analysis between boys (n = 214) and girls (n = 382), type 1 diabetes was more common (12% vs 6%, P = .013) and hemoglobin higher (median 126 g/L vs 123 g/L, P = .016) in boys. There were no significant differences between the sexes in any of the other study variables.

The annual incidence of CDA in the hospital catchment area varied between 31 and 57 cases per 100 000 in 2001-2013 (incidence rate ratio 1.03, P = .005). This increased in 2001-2007, since then the figures have fluctuated without systematic trend (**Figure 2**; available at www.jpeds.com).

Discussion

During the past few decades, a number of studies, mostly from developed countries, have reported changes toward a milder clinical picture and an increasing incidence of celiac disease.[2,3,9-11,14,33] We confirmed a similar trend in these respects and found an amelioration in the histologic damage. In this long-term study, the most prominent changes were seen in the 1980s and 1990s, and subsequently most of these seemed to reach a plateau.

The most significant changes in the clinical presentation occurred at the turn of the 21st century, when the

Table II. Age at the time of celiac disease diagnosis and distribution of symptoms (%) in 292 children with gastrointestinal complaints as the main clinical presentation of celiac disease divided into 4 periods based on year of diagnosis

	<1980, n = 26	1980-1999, n = 41	2000-2009, n = 148	2010-2013, n = 77	*P* value*
Age, median (Q_1, Q_3), y	4.4 (1.1, 12.1)	7.0 (2.0, 12.7)	7.8 (5.0, 11.7)	7.4 (4.4, 10.6)	.101
Diarrhea	69	78	50	53	.008
Vomiting	27	32	6	2	<.001
Abdominal pain	50	61	75	84	.003
Constipation	4	2	21	27	.002

**P* value denotes statistical difference among the 4 periods.

proportions of screen-detected and asymptomatic children increased over 6-fold and simultaneously gastrointestinal symptoms of diarrhea and vomiting decreased and milder or more atypical symptoms increased. The plateau in these after the 1990s has not been reported before, but changes toward a less severe overall presentation in celiac disease have already been observed previously.[2,9-11,14,33,34] However, thus far, it has been difficult to discern precise secular trends, as most previous studies have covered either a relatively short period of time or small numbers of patients. In addition, comparisons have usually been made only between 2 different time-spans or between newly diagnosed patients and literature-based historical controls; varying definitions of celiac disease-related terms have further complicated interpretation of results.[2,3,9,10,13,14,33,34] Hence, a major strength of our study was the extended time-frame covering almost the entire history of modern, histologically defined celiac disease. Furthermore, even if the study cannot be considered truly prospective, it must be emphasized that almost all of the diagnoses were made by the authors themselves or under their supervision. A limitation, on the other hand, is that our database does not include all children diagnosed during the study period, in particular from the era before the 2000s.

Concomitant with the clinical presentation, the severity of the small-bowel mucosal damage became milder after the 1990s and then reached a plateau. The few previous studies investigating this issue have described a similar trend toward less severe villous atrophy.[2,14,33] In accordance with our findings, Gokce et al[34] observed an unchanging histologic presentation of celiac disease in children diagnosed between 2005 and 2012. In the present long-term study, we report both the earlier amelioration and the subsequent plateau in the severity of mucosal damage. Nevertheless, it must be emphasized that in the earlier series specimens were obtained by jejunal capsule and may not, thus, be fully comparable with later biopsies taken upon gastrointestinal endoscopy.

Table III. Severity of clinical presentation and degree of small-bowel mucosal villous atrophy in 292 children with gastrointestinal complaints as the main presentation of celiac disease divided into 4 periods based on year of diagnosis

	<1980, n = 26	1980-1999, n = 41	2000-2009, n = 148	2010-2013, n = 77	*P* value*
Severity of clinical presentation, %					.002
Mild	23	42	45	69	
Moderate	62	51	48	25	
Severe	15	7	7	6	
Degree of villous atrophy, %					<.001
PVA	14	11	44	39	
SVA	32	33	40	44	
TVA	55	56	16	17	

**P* value denotes statistical difference among the 4 periods.

In contrast to most of the changes in clinical presentation, poor growth became rarer and the clinical presentation milder in 2010-2013. In some respects, including sex distribution and presence of anemia, there were no major secular changes, or they fluctuated without clear trend. In the case of anemia, this might be partly explained by the fact that previously the disorder was usually the result of severe malabsorptive disease, whereas nowadays celiac disease is actively sought in children with unexplained anemia.[25] More intensive screening could also explain the slight increase in the incidence of anemia in 2010-2013. There were also no significant changes in the prevalence of associated diseases; this, however, is likely due to the small number of cases, as there was a 5-fold increase in type 1 diabetes in the 1980s and a corresponding decrease in thyroid disease. These observations could be explained by the regular screening for celiac disease in children with diabetes already initiated in Finland in the 1980s, and by the disappearance of the previously common iodine deficiency.

The incidence of CDA increased in the early 2000s and thereafter remained more or less stable. Although inquiry into this was limited to clinically detected patients and most recent time-points, it is noteworthy that the possible plateau occurred simultaneously with the recently reported leveling off in the incidence of type 1 diabetes; parallel changes in these diseases have also been previously reported.[17,23,24] In other countries, the overall incidence of pediatric celiac disease has mainly increased, except among young children.[3,4,35-37] The increase in the age at diagnosis after 1980 could be explained mostly by the decreased proportion of the youngest patients. Interestingly, a completely opposite phenomenon was observed in Sweden in the late 1980s and early 1990s, when there was a true epidemic of celiac disease in infants.[7,36,38] This was attributed to a change in the popularity and duration of breast-feeding and the

amount and the age at introduction of gluten into the diet.[7,36,38-40] However, the precise role of these environmental factors remains unclear and was not confirmed in recent prospective studies.[41-43]

Improved diagnostic methods and increased knowledge probably explain most of the changes seen in the clinical and histologic presentation and incidence of celiac disease. Sensitive serologic tests have made screening easier, and new diagnostic guidelines and more readily available information have increased awareness among physicians and the general population.[25,44,45] Nevertheless, the well-defined increase in the true prevalence of celiac disease,[3,17,18] the above-described Swedish epidemic, and the fact that here also the classical presentation has become milder are difficult to explain solely by improved diagnostics. Simultaneous changes in incidence and presentation among related diseases, including type 1 diabetes and inflammatory bowel disease, in which especially in type 1 diabetes the diagnostics have remained relatively unchanged, further support the role of environmental factors.[19-21] In addition to diabetes, the previously noted increase in the incidence of inflammatory bowel disease might have levelled off.[22] In celiac disease, the plateau now observed could be a result of unchanged diagnostics and environmental factors in developed countries during the 21st century, while in developing countries the disease is still rapidly changing.[46] The role of the environment is further supported by major differences in the true prevalence of the disease between Finland and Russian Karelia, where the populations share similar genotypes and consumption of cereals but live in different socioeconomic environments.[15] Higher socioeconomic status was also associated with a higher celiac disease risk in another recent study.[47] More research is evidently needed to discern the true role of environmental factors in celiac disease.

In conclusion, our study covering a period of almost 50 years showed that most of the changes observed in the presentation and incidence of pediatric celiac disease may have reached a plateau. The majority of these secular variations are probably explained by changes in the diagnostics and awareness of the disease, but environmental factors may also have a role. ■

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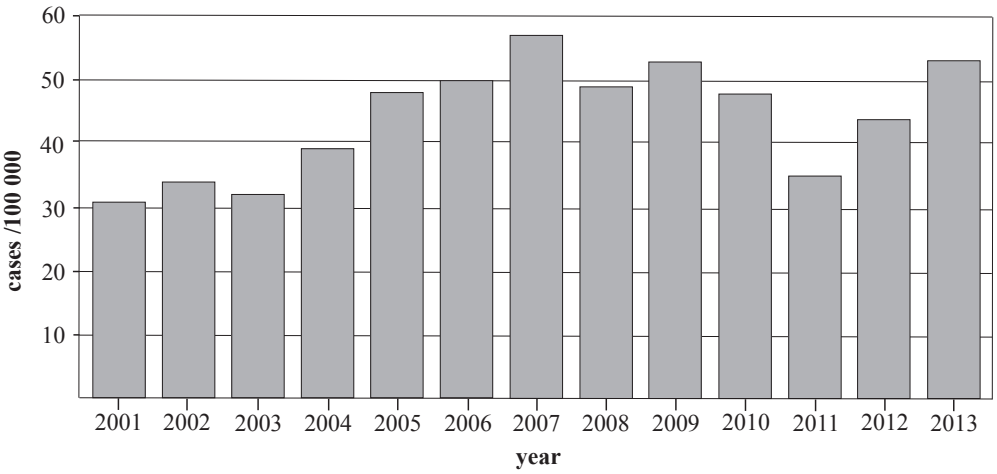

Figure 2. Annual incidence of children with positive tissue transglutaminase or EmAs admitted to Tampere University Hospital during 2001-2013 because of celiac disease suspicion.

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

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Objective To assess whether children at risk for celiac disease should be screened systematically by comparing their baseline and follow-up characteristics to patients detected because of clinical suspicion.

Study design Five hundred four children with celiac disease were divided into screen-detected (n = 145) and clinically detected cohorts (n = 359). The groups were compared for clinical, serologic, and histologic characteristics and laboratory values. Follow-up data regarding adherence and response to gluten-free diet were compared. Subgroup analyses were made between asymptomatic and symptomatic screen-detected patients.

Results Of screen-detected patients, 51.8% had symptoms at diagnosis, although these were milder than in clinically detected children ($P < .001$). Anemia (7.1% vs 22.9%, $P < .001$) and poor growth (15.7% vs 36.9%, $P < .001$) were more common, and hemoglobin (126 g/l vs 124 g/l, $P = .008$) and albumin (41.0 g/l vs 38.0 g/l, $P = .016$) were lower in clinically detected patients. There were no differences in serology or histology between the groups. Screen-detected children had better dietary adherence (91.2% vs 83.2%, $P = .047$). The groups showed equal clinical response (97.5% vs 96.2%, $P = .766$) to the gluten-free diet. In subgroup analysis among screen-detected children, asymptomatic patients were older than symptomatic (9.0 vs 5.8 years of age, $P = .007$), but the groups were comparable in other variables.

Conclusions More than one-half of the screen-detected patients with celiac disease had symptoms unrecognized at diagnosis. The severity of histologic damage, antibody levels, dietary adherence, and response to treatment in screen-detected cases is comparable with those detected on a clinical basis. The results support active screening for celiac disease among at-risk children. *(J Pediatr 2017;183:115-21).*

Celiac disease has become a major public health issue with an estimated prevalence of 1%-3% in many Western and Asian countries.[1-3] However, because of the variable gastrointestinal and extra-intestinal symptoms involved, the majority of affected children remain unrecognized.[1,2] Because screening for the disease is available by antibody tests, it has been suggested that diagnostic rates can be increased through screening either known at-risk groups[4-6] or the entire population.[7] However, although celiac disease fulfils several World Health Organization criteria for population screening, the benefits of this approach remain controversial.[8,9] In particular, it remains unclear how well mildly symptomatic or asymptomatic screen-detected patients will adhere to a demanding and socially restrictive gluten-free diet.[6,10-17] Although untreated celiac disease predisposes to severe complications with increased use of healthcare services in symptomatic patients,[9,18,19] it is not known whether this applies to screen-detected individuals, who may possible have less severe histologic damage[20] and, consequently, better long-term outcome. Then again, complications such as poor growth, dental enamel defects, and low bone mass have been observed even in otherwise asymptomatic children with celiac disease, and these maladies may remain permanent if left untreated.[21-23]

To evaluate the potential benefits and detriments of celiac disease screening, we compared clinical, serologic, and histologic features and follow-up results between children detected during the course of risk-group screening and those identified on clinical suspicion.

EmA	Endomysial antibody
Rf	Reference value
T1DM	Type 1 diabetes mellitus
TG2ab	Transglutaminase 2 antibody

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Portions of the study were presented at the 16th International Celiac Disease Symposium, Prague, Czech Republic, June 21-24, 2015; and as a poster at the annual meeting of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition, Athens, Greece, May 25-28, 2016.

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Methods

The study was conducted at the Tampere Center for Child Health Research, University of Tampere and Tampere University Hospital, and at the Department of Pediatrics, Tampere University Hospital. Patient data were collected from our research database, which contains medical information on children diagnosed with celiac disease from the late 1960s to the present. Lacking or incomplete patient information has been supplemented with personal or telephone interviews by an experienced physician or study nurse. From the year 2012 onward, most of the database patients have participated in a prospective study enrolment. To increase the integrity of the results, only children diagnosed from the year 2000 onward were included. Exclusion criteria were age ≥18 years, unclear diagnosis of celiac disease, and lack of data regarding the initial clinical presentation. Altogether, 504 children with celiac disease proven by biopsy comprised the final study cohort.

The following celiac disease-related information was collected on each child at the time of the diagnosis: clinical characteristics, severity of histologic damage, celiac disease serology, a variety of other laboratory variables, and presence of celiac disease in the family. Follow-up data regarding adherence and clinical and serologic response to the gluten-free diet were recorded. The results were compared between children detected by screening and those found on the basis of clinical suspicion. For the corresponding subgroup analysis, screen-detected children were further divided into asymptomatic and symptomatic patients.

The Pediatric Clinic of Tampere University Hospital and the Ethics Committee of the Pirkanmaa Hospital District, Tampere, Finland, approved the study. Written informed consent was obtained from all subjects and/or their parents participating in the personal interviews or prospective study enrollment.

Screen-detected patients included at-risk children such as those with celiac disease in relatives (first degree or more distant), type 1 diabetes mellitus (T1DM), or autoimmune thyroidal disease as a comorbidity. Some patients were screened for celiac disease because of attendance in a follow-up study attributable to increased genetic risk for T1DM. Clinically detected children were diagnosed on the basis of gastrointestinal or extra-intestinal symptoms or findings, including diarrhea, abdominal pain, constipation, arthralgia, dermatitis herpetiformis, anemia, and poor growth. Severity of symptoms was classified as no symptoms; mild symptoms (occasionally disturbing minor symptoms); moderate symptoms (more frequent and distracting symptoms); and severe symptoms (distracting symptoms causing recurrent nighttime awakenings, school absence, etc). Anemia and poor growth were considered as findings or complications of celiac disease and were, thus, not included in the classification of symptoms. Height and weight at the diagnosis were noted and expressed in age- and sex-dependent SD units. Poor growth was defined based on abnormalities in expected height and growth velocity as described elsewhere.[23,24] Body mass index was calculated as weight/height^2 (kg/m^2).

Small-Bowel Mucosal Damage and Laboratory Variables

At least 4 distal duodenal mucosal samples were taken during gastrointestinal endoscopy in all children with suspected celiac disease. From 2012 onward, samples were also obtained from the duodenal bulb.[25] The severity of mucosal damage was assessed from several well-orientated biopsy sections[26] and further categorized as mild (Marsh IIIa), moderate (Marsh IIIb), or total villous atrophy (Marsh IIIc).

Transglutaminase 2 antibodies (TG2ab) were measured by either automatized automated enzyme fluoroimmunoassay assay (Phadia AB, Uppsala, Sweden), or before 2011 by conventional enzyme-linked immunosorbent assay (Phadia). Values 7 U/L or higher for TG2ab are considered positive; 120 U/L is the highest reported value. Serum endomysial antibodies (EmAs) were measured by indirect immunofluorescence as previously described.[20,27] A dilution of 1: ≥5 for EmA was considered positive and further diluted up to 1:4000 or until negative.

Results of the following laboratory tests were collected on each child when available: hemoglobin (g/L), erythrocyte mean corpuscular volume (reference value [Rf] 73-95 fL), plasma albumin (Rf 36-48 g/L), plasma transferrin receptor (TfR) (age- and sex-matched Rf),[28] plasma ferritin (Rf >20 μg/L), plasma alanine aminotransferase (Rf ≤30 U/L),[29] and plasma thyroid-stimulating hormone (TSH) (Rf 0.27-4.2 mU/L). Anemia was defined as a hemoglobin value below the age- and sex-matched reference.[30] For consistency, only laboratory values taken at the time of diagnostic evaluations were accepted for the baseline comparisons. Values other than hemoglobin were systematically obtained only during the latter part of the study period.

Follow-Up Investigations

All children initiated a gluten-free diet shortly after the diagnosis under the supervision of a qualified dietitian. Adherence to the diet was assessed during each follow-up visit based on self-reported gluten avoidance and results of serology, and categorized into strict diet, occasional lapses, and no diet. Clinical and serologic response to the dietary treatment was also evaluated and classified as (1) good response (disappearance of symptoms and normalized or markedly decreased celiac antibody levels); or (2) no response (persistent symptoms and/or antibody positivity). Routine follow-up visits took place approximately 3-6 and 10-12 months after the celiac disease diagnosis. Further, 120 of the children were interviewed after a median of 4 years from the diagnosis. Results of follow-up serology were analyzed by comparing the baseline TG2ab values with those measured after a median of 13 (range 6-24) months on a gluten-free diet.

Statistical Analyses

Categorized variables are reported as percentage distributions and numeric variables as medians with quartiles. Fisher exact test or χ^2 test was used to compare categorized variables and Mann-Whitney U test with numeric variables. Binary logistic regression was used to adjust age differences between the groups. A P value of <.05 was considered significant.

Analyses were performed with SPSS v 22 (IBM Corporation, Armonk, New York).

Results

Altogether, 145 (28.8%) children were detected by screening and 359 (71.2%) on a clinical basis (**Table I**). The main presentation was gastrointestinal in 68.0% and extra-intestinal in 32.0% of the patients detected because of symptoms. There were no differences between screen- and clinically detected children in age or sex, but celiac disease in first-degree relatives and concomitant T1DM were more common among the screen-detected children (**Table I**); these were also the primary reasons for screening. More clinically detected patients had anemia and poor growth, but these disorders were also seen in a substantial proportion of those identified by screening (**Table I**).

Furthermore, 51.8% of the screen-detected children reported symptoms at diagnosis, usually less severe than in patients diagnosed clinically (**Figure 1**, A-B; available at www.jpeds.com). Diarrhea or loose stools were more common among clinically detected patients, but otherwise the groups did not differ in the distribution of symptoms (**Table II**; available at www.jpeds.com). There were no significant differences between the study groups in anthropometric measurements (**Table III**) or severity of histologic damage (**Figure 1**, C). In 3 screen-detected and in 10 clinically detected children, the celiac disease diagnosis was based on lesions in the duodenal bulb only ($P = 1.000$). The median blood hemoglobin and serum albumin were slightly lower among clinically detected subjects (**Table III**), but except for anemia, the prevalence of abnormal laboratory values did not differ between the groups (clinically vs screen-detected): low albumin 23.0% vs 10.5%, $P = .343$; erythrocyte mean corpuscular volume 10.6% vs 13.4%, $P = .515$; and ferritin 20.5% vs 20.0% $P = .958$; and increased plasma transferrin receptor 31.3% vs 22.2%, $P = .451$; plasma alanine aminotransferase 15.6% vs 16.0%, $P = 1.000$; and plasma thyroid-stimulating hormone 14.2% vs 7.3%, $P = .251$, respectively.

Adherence to a gluten-free diet was better among the screen-detected children (**Figure 1**, D). However, there was no significant association between the presence of strict adherence and celiac disease in the family (celiac disease 81.3% vs no disease 90.4%, $P = .060$) or concomitant T1DM in the child (T1DM 85.8% vs no T1DM 84.6%, $P = .835$). The clinical and serologic response were equally good in both groups (97.5% vs 96.2%, $P = .766$). Similarly, while on diet serum TG2abs decreased in all but 2 screen-detected and in all clinically detected patients (**Figure 2**). On later follow-up, the antibodies declined in the 2 cases with no initial response (data not shown). The median time on a gluten-free diet before the follow-up TG2ab measurement was comparable between the screen-detected and clinically detected children (12.0 vs 11.0 months, $P = .090$).

Among the screen-detected patients, symptomatic children were significantly younger and had higher EmA and lower median hemoglobin compared with those who were asymptomatic upon crude analysis, but the differences were no longer significant when adjusted for age (**Table IV**). There were no differences between the subgroups in sex, growth variables or presence of anemia, concomitant T1DM and celiac disease in relatives (**Table IV**), or prevalence of abnormal laboratory values (data not shown). Further, the screen-detected groups were comparable in severity of histologic damage and dietary adherence (**Figure 3**; available at www.jpeds.com).

There was no association between EmA or TG2ab levels and the severity of villous atrophy in screen-detected patients (median EmA titers Marsh IIIa = 1:200, IIIb = 1:500, IIIc = 1:500, $P = .164$; TG2ab levels 86.0 U/L, 114.0 U/L, and 113.0 U/L, respectively, $P = .318$), whereas the association was seen when evaluated in the whole group (EmA 1:200, 1:500 and 1:1000, $P < .001$; TG2ab 72.0 U/L, 120.0 U/L, 120.0 U/L, $P < .001$).

Discussion

The present study demonstrated that even screen-detected children often have unrecognized clinical symptoms and signs of celiac disease before diagnosis. Furthermore, these patients are

Table I. Demographic data and clinical characteristics in 504 children diagnosed with celiac disease by screening in at-risk groups or based on clinical suspicion

	Screen-detected (n = 145)		Clinically detected (n = 359)		
	n	%	n	%	*P* value*
Age at diagnosis, median (Q_1, Q_3), y	145	7.0 (4.1, 11.7)	359	8.0 (5.0, 11.7)	.202
Girls	90	62.1	239	66.6	.336
Celiac disease in the family	55†	59.8	72‡	33.8	<.001
Type 1 diabetes	32	22.2	7	2.2	<.001
Thyroidal disease	2	1.4	5	1.6	1.000
Down syndrome	0	0.0	4	1.3	.314
Anemia at diagnosis	10	7.1	72	22.9	<.001
Poor growth at diagnosis	22	15.7	117	36.9	<.001

Q_1 and Q_3, lower and upper quartiles.
*χ^2 test, Fisher exact test, and Mann-Whitney U test.
Data available >85% of the patients, except in †92 and ‡213.

Table III. Laboratory values and growth measures at celiac disease diagnosis in 504 children diagnosed by screening in at-risk groups or based on clinical suspicion

	Screen-detected (n = 145)		Clinically detected (n = 359)		
	n*	Median (Q_1, Q_3)	n*	Median (Q_1, Q_3)	*P* value†
EmA, titer	103	1:500 (1:100, 1:2000)	247	1:500 (1:100, 1:1000)	.576
Hemoglobin, g/L	81	126 (121, 135)	258	124 (112, 131)	.008
Mean corpuscular volume, fL	67	81.0 (76.0, 84.0)	227	80.5 (76.0, 83.0)	.595
Albumin, g/L	19	41.0 (38.0, 42.0)	74	38.0 (36.8, 40.0)	.016
Transferrin receptor, mg/L	18	4.5 (3.1, 6.1)	67	4.4 (3.5, 6.5)	.763
Ferritin, μg/L	25	10.0 (6.0, 17.0)	83	13.0 (7.0, 23.0)	.468
Alanine aminotransferase, U/L	25	20.0 (16.0, 25.5)	122	20.0 (16.0, 26.0)	.903
Thyroid-stimulating hormone, mU/L	41	2.0 (1.5, 3.2)	120	2.5 (1.7, 3.3)	.212
Height, SD	87	0.3 (–0.5, 1.2)	170	0.0 (–0.8, 0.9)	.242
Weight, SD	66	–0.4 (–1.0, 0.5)	133	–0.3 (–1.3, 0.5)	.695
Body mass index, kg/m^2	80	16.3 (15.0, 18.0)	167	16.3 (14.9, 18.6)	.808

*Data available.
†Mann-Whitney U test.

comparable with those found on clinical basis with respect to histologic and serologic markers of disease severity and have better adherence and response to the gluten-free diet. Our findings support active screening of celiac disease among at-risk children. Conversely, the benefits of screening the general population remain obscure.

Over one-half of the screen-detected children reported gluten-responsive symptoms, which had neither led to a doctor visit nor been recognized as celiac disease in clinical practice. In line with this, recent studies conducted among screened children and adults have shown 34%-84% of such patients suffer from unrecognized symptoms at the time of the celiac disease diagnosis.[11,15,31,32] These findings demonstrate that symptom-based case finding may not even detect a number of children with classical gastrointestinal manifestations, let alone those who present with atypical or subtle symptoms. What is more, most of the above mentioned pediatric screening studies have been conducted in Finland and other Nordic countries, where the disease is fairly well-known among pediatricians and primary care physicians,[15,32] and in other countries, the situation might

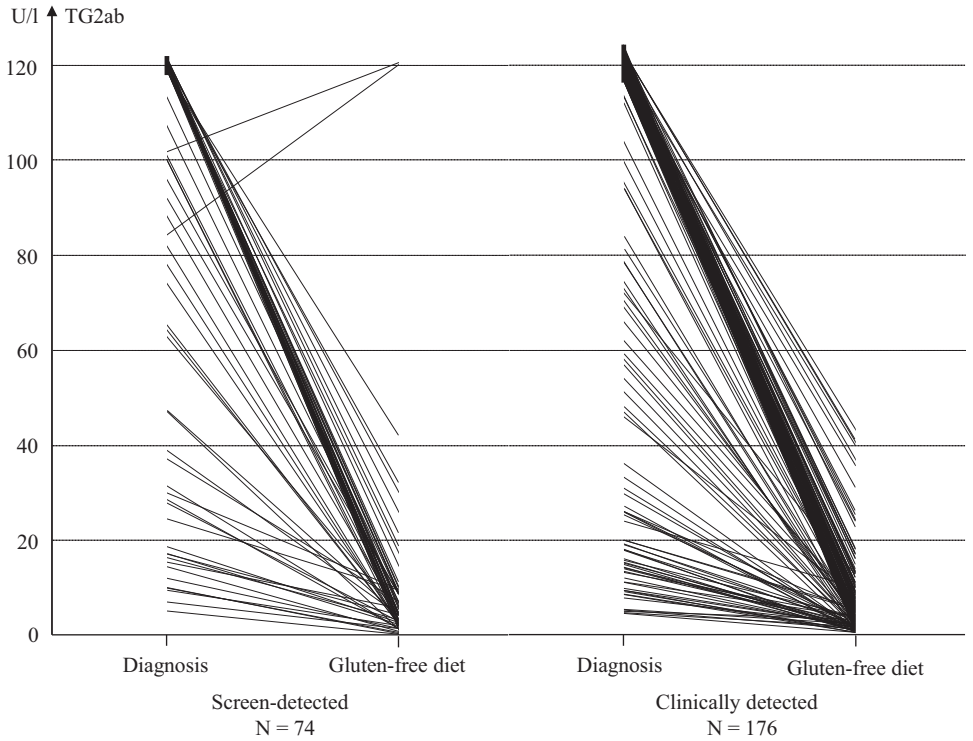

Figure 2. Transglutaminase 2 antibody values at the time of diagnosis and on a gluten-free diet in 250 children diagnosed with celiac disease by either at-risk screening or based on clinical suspicion.

Table IV. Clinical characteristics, laboratory values, and growth measures in 139 children with screen-detected celiac disease divided into two groups based on the presence or absence of symptoms at diagnosis

	Asymptomatic screen-detected (n = 67)		Symptomatic screen-detected (n = 72)		
	n	%	n	%	*P* value *
Girls	42	62.7	45	62.5	.982
Celiac disease in the family	23†	54.8	31‡	68.9	.175
Type 1 diabetes	18	26.9	11	15.5	.101
Anemia at diagnosis	3	4.7	4	5.6	1.000
Poor growth at diagnosis	11	16.9	9	12.9	.506
	n§	Median (Q_1, Q_3)	n§	Median (Q_1, Q_3)	
Age at diagnosis, y	67	9.0 (4.9, 12.0)	72	5.8 (3.9, 10.0)	.007
EmA, titer	53	1:200 (1:100, 1:1000)	45	1:1000 (1:200, 1:4000)	.032¶
Hemoglobin, g/L	36	132 (123, 136)	39	124 (117, 130)	.010**
Height, SD	43	0.3 (–0.7, 1.2)	39	0.2 (–0.4, 1.2)	.838
Weight, SD	33	–0.5 (–1.1, 0.9)	29	–0.3 (–1.1, 0.3)	.651
Body mass index, kg/m^2	43	16.0 (15.1, 18.1)	33	16.4 (14.8, 17.8)	.604

*χ^2 test, Fisher exact test, and Mann-Whitney U test.
Data was available in >95% of the patients in each variable presented in percentages except in †42/67 and ‡45/72. With quantitative values (§) the number of available data is reported in the column below.
P values when adjusted for age using binary logistic regression: ¶0.076 and **0.233.

be even poorer. For example, in the US only 17% of all patients with celiac disease were aware of their disorder before population screening,[33] and underdiagnosis has also been observed in New Zealand and Australia.[34]

Besides unrecognized symptoms, many of the screen-detected children suffered from poor growth and anemia, which were not recognized as a sign of celiac disease before the screening. There has been debate as to whether the risk of long-term complications is similar among screen- and clinically detected patients,[9,18] but data actually comparing these 2 groups are limited. Previously Korponay-Szabó et al[35] reported a prevalence of 22% for anemia and 31% for poor growth in a population-based cohort of screen-detected schoolchildren in Hungary. We have also shown these features to be present in otherwise asymptomatic patients,[23,36] and there is some evidence that the introduction of a gluten-free diet can improve growth and hemoglobin values in screen-detected children.[37] Other possible complications, which have been observed regardless of the clinical presentation of celiac disease, are low bone mineral density, dental enamel defects, and elevated transaminases.[21,22,29,38]

In support of the presence of advanced disease and risk of complications, the screen-detected children had levels of celiac disease autoantibodies and severity of villous atrophy similar to those detected on a clinical basis. It is possible that, despite equal severity of histologic injury, the clinically detected group had longer length of small intestinal injury, which may explain their apparent gastrointestinal symptoms.[39] However, current evidence in adults does not support this hypothesis.[40] Earlier studies have yielded inconsistent results on the correlation between clinical picture and histologic findings in celiac disease.[20,41-43] Apart from differences in study designs, these discrepancies might be at least partly explained by differences in clinical presentation of the disease between countries. Studies from many developed countries have reported that the severity of celiac disease is becoming milder even in the subgroup of patients suffering from classic gastrointestinal symptoms.[44,45] This may contribute to the increasing similarity between clinically and screen-detected children. Nevertheless, in favor of early diagnosis and treatment, more than one-half of the children in both groups already had either moderate or total villous atrophy at diagnosis.

To justify screening, we consider it of prime importance that compliance with the gluten-free diet is comparable among screen- and symptom-detected children. In support of excellent dietary adherence, the study groups showed equal clinical and serologic response to the diet. Although not all had complete normalization of antibodies during follow-up, a similar slow response in some patients with celiac disease has been noted elsewhere.[12,37] The present study confirmed the results of our previous survey-based study, in which the diagnostic approach had no effect on dietary adherence,[15] and similar observations have recently been reported from The Netherlands and Sweden.[12,14] In contrast, in an earlier Italian study, only 23% of screen-detected adolescents had satisfactory adherence to a gluten-free diet 5 years after the celiac disease diagnosis.[10] However, these patients were found by population-based mass screening. Additional explanations for variable adherence might be differences in the availability and cost of gluten-free products in many countries and in awareness of celiac disease, for example, in restaurants.[46] In Finland and some other countries, governments financially support every child with confirmed celiac disease,[47] although this was also the case in the above-mentioned Italian study showing poor adherence.[10] Other factors likely affecting dietary adherence include the intensity and organization of follow-up, the availability of a dietician, the presence of comorbidities, and celiac disease in other family members.[13,16,48] Of note, we found no association between the adherence and presence of concomitant T1DM in the child or celiac disease in the family. Regardless, our results demonstrate

that excellent adherence to the gluten-free diet is attainable in screen-detected patients with celiac disease diagnosed and followed in a well-organized clinical practice.

Even if the benefits of the gluten-free diet in the present and some earlier studies favor screening and active treatment of celiac disease,[6,15,17,31] there is reason for caution. Besides the social restrictions and economic burden,[6,11,49] it is possible that the diet predisposes some patients to suboptimal intake of vitamins and trace elements and to obesity.[50,51] Furthermore, despite the promising short-term results, there is a risk that dietary adherence will decline in adolescence and adulthood, when follow-up usually becomes less frequent and responsibility for daily treatment shifts from the parents to the patients themselves. This issue has been scantily studied, but Van Koppen et al[14] reported good adherence and improved health in a majority of screen-detected children 10 years after diagnosis. In contrast, in an earlier study by O'Leary et al[52] only 50% of the patients with celiac disease diagnosed in childhood remained on a strict gluten-free diet after a median of 28 years of follow-up. In adults, dietary lapses have been a problem particularly in asymptomatic patients,[11] whereas this was not the case in the present study. More studies evaluating dietary adherence and the benefits of a gluten-free diet in the long term in screen-detected children are required.

The main strengths of the present study were the large cohort of patients with celiac disease diagnosed on uniform nationwide criteria, and the wide array of serologic and histologic variables assessed. In addition, follow-up data regarding adherence and clinical and serologic response to the gluten-free diet were documented in the majority of the children. The main limitations include the retrospective design, lack of systematic collection of laboratory variables other than serology during the whole study period and the lack of structured questionnaire for collection of symptoms, and dietary adherence. Further, the median follow-up time in the study was too short to estimate long-term dietary adherence and the effects of an early initiated gluten-free diet on the possible complications and comorbidities of celiac disease.

In conclusion, the high percentage of unrecognized clinical symptoms and excellent response and adherence to the gluten-free diet support active screening of celiac disease in at-risk children. An alternative option might be low-threshold case finding among at-risk children, but it is important to realize that even apparently asymptomatic patients may have well-advanced serologic and histologic disease and a subsequent risk of long-term complications. ■

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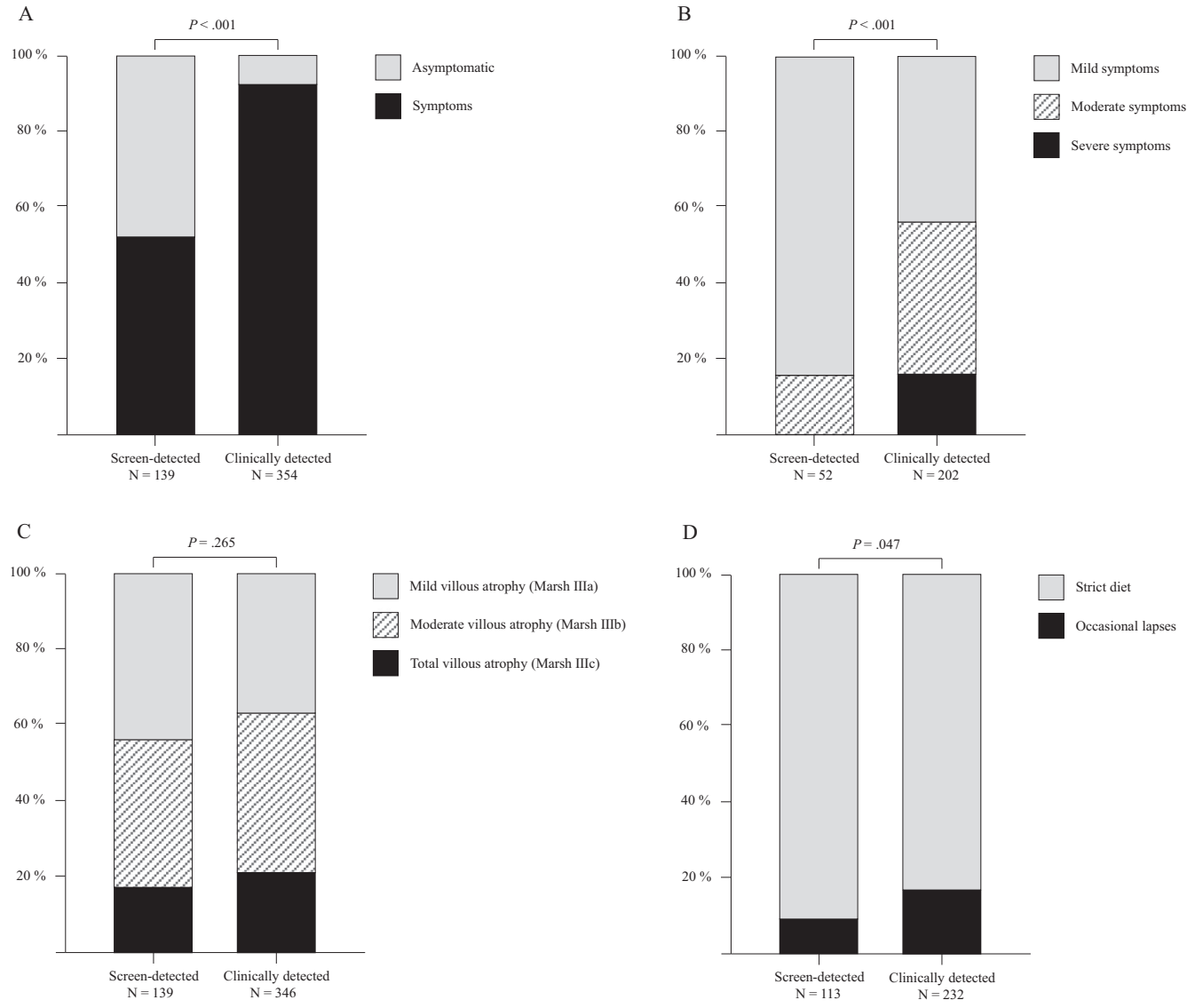

Figure 1. **A,** Presence and **B,** severity of clinical symptoms, **C,** degree of small-bowel mucosal villous atrophy and **D,** adherence to the gluten-free diet in 504 children diagnosed with celiac disease either by screening or upon clinical suspicion. Asymptomatic patients are excluded from **B**.

Table II. Distribution of symptoms at diagnosis in 398 screen-detected and clinically detected children with celiac disease

	Screen-detected (n = 72)		Clinically detected (n = 326)		
	n*	%	n*	%	*P* value†
Stomach pain	61	55.7	295	65.4	.152
Diarrhea or loose stools	63	28.6	277	42.2	.045
Constipation	62	25.8	272	21.3	.443
Skin symptoms	72	9.7	325	6.2	.300
Arthralgia	72	2.8	326	7.7	.194

*Data available.
†χ^2 test and Fisher exact test.

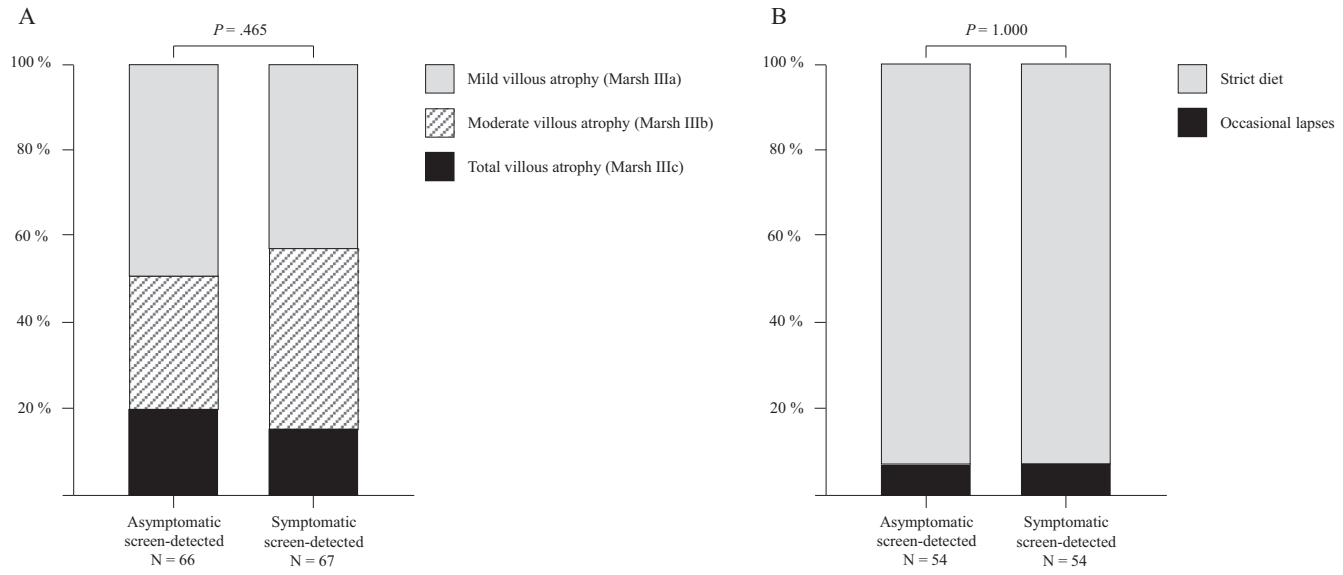

Figure 3. **A,** Degree of small-bowel mucosal villous atrophy and **B,** adherence to the gluten-free diet in 139 screen-detected children with celiac disease divided into 2 groups based on the presence or absence of clinical symptoms at diagnosis.

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

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Abstract

Background: The diagnostic yield of coeliac 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 coeliac patients diagnosed in childhood by screening.

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

Results: In total, 236 (42%) patients completed the questionnaires a median of 18.5 years after childhood diagnosis. Screen-detected patients ($n = 48$) had coeliac disease in the family and type 1 diabetes more often, and were less often smokers and members of coeliac 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 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 coeliac disease. However, asymptomatic patients may require special attention.

Keywords

Children, diagnosis, gluten-free diet, long-term follow-up, quality of life, screening

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Key summary

Established knowledge on this subject

- Coeliac 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.

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New findings of this study

- Adult Celiac disease patients diagnosed by screening in childhood were comparable to those found because of clinical suspicion in a variety of health outcomes, including adherence to a 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

Over recent decades, coeliac 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 coeliac 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 is some evidence from short-term follow-up studies that these children can achieve good dietary adherence and quality of life.[7,10–12] However, long-term data in screen-detected coeliac 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 coeliac 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 coeliac disease in the patient records of Tampere University Hospital, (Figure 1) a tertiary center with a catchment area of ≈120,000 children. Patients who were diagnosed <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 to 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 2 months (Figure 1).

For the subsequent analyses, the responders were divided into: (a) those diagnosed via risk-group screening including patients suffering from type 1 diabetes or other concomitant autoimmune disease, or having relatives with coeliac disease, and (b) 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

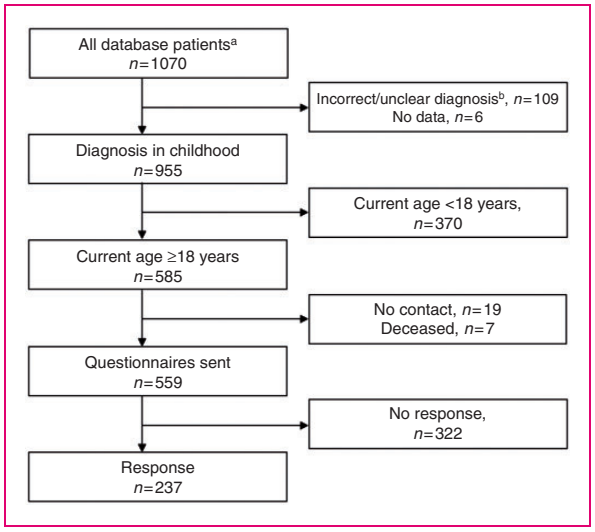

Figure 1. Flowchart of the study.
[a]Patients were gathered from our research database and supplemented by a search in the patient records with ICD-7-10 diagnosis codes K90.0, 579A, 579.0, 269.00, 269.98 and 286.00 possibly indicating coeliac disease.
[b]Patients with an incorrect diagnosis code were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

initiation of a 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 coeliac disease patients. None of the controls had suspicion of coeliac disease or known coeliac disease in close relatives.

Medical history

Medical data were collected regarding the clinical and histological presentation of coeliac disease at the time of diagnosis. Information was gathered on the main reason for coeliac disease suspicion and presence of gastrointestinal or extra-intestinal symptoms. Furthermore, possible complications, as well as the presence of coeliac disease-related or other coexisting diseases, and coeliac disease in first-degree relatives were noted. Abnormalities in laboratory values or physicians' examinations 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). Anaemia at diagnosis was defined based on the age- and gender-dependent reference values for haemoglobin.

Severity of histological damage was classified based on the pathological 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

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 socio-demographic and lifestyle characteristics such as work and study situation, membership of a coeliac society, regularity of physical exercise, smoking, the presence of children and coeliac disease in the family. The presence of coeliac-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 their experiences of self-assessed possibly coeliac 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 the 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, with higher scores representing better well-being. The total score is the sum of all scores, with the values being between 22 and 132, and the subdimensions are calculated as sums of scores of selected questions. For example, vitality describes a person's energy level, and the score represents the sum of questions about overall energy, activity, tiredness, and experience of resting after a night's sleep.[20]

The Gastrointestinal Symptom Rating Scale (GSRS) consists of 15 questions, which evaluate common gastrointestinal symptoms and their severity.[21] Each question is scored via a seven-point Likert scale from asymptomatic (1) to severe symptoms (7). The total score is calculated as a mean of all 15 items. Further, the questions are divided to five subdimensions – abdominal pain, indigestion, diarrhoea, 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, 31 May 2016), and ethical guidelines of the 1975 Declaration of Helsinki were followed. Patients participating in 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 tests. Bonferroni correction was used in pair-wise post hoc comparisons. Categorized values are reported as numbers and percentages, and compared via χ^2 or Fisher's exact tests. Significance was set at p value < 0.05. Statistical analyses were carried out with SPSS version 23 (IBM Corporation, Armonk, NY). Data were available for $> 90\%$ of patients unless otherwise stated.

Results

Altogether, 237 (42%) currently adult patients answered the questionnaires (Figure 1). The responders were more often girls, suffered type 1 diabetes less frequently and had more coeliac disease in the family than

Table 1. Characteristics at time of childhood diagnosis in currently adult coeliac 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
Anaemia, no. (%)	9 (18.8)	54 (31.2)	0.091
Haemoglobin, 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, anaemia and other laboratory abnormalities excluded.
[b]Data available from 32 patients only.
[c]Data available from 158 patients only.
[d]Data available from 168 patients only.
IQR: interquartile range; no.: number.

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 evaluation (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 a significantly older age and more recently. They also had fewer symptoms and growth disturbances at diagnosis, but although their haemoglobin levels were higher, there was no significant difference between the groups in the presence of anaemia. 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 years, $p = 0.098$) and more often girls (86 vs 56%, $p = 0.025$), and had more anaemia (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 haemoglobin or degree of villous atrophy (data not shown).

In current comparison at a median of 18.5 years (interquartile range = 12.7, 30.7 years) after the diagnosis, the presence of coeliac disease in the family and type 1 diabetes were more common in screen-detected patients, whereas they were less often members of coeliac societies or current smokers than those found due to clinical suspicion (Table 2). The groups were comparable in age, work and study situation, the 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 the implementation of follow-up (Table 3). There were no differences between the subgroups of symptomatic and asymptomatic patients in the aforementioned variables (Table 4).

Screen-detected and clinically-detected patients were comparable with respect to current quality of life and symptoms as measured by PGWB and GSRS, but both groups showed lower vitality (Figure 2(a)), and screen-detected patients reported more abdominal pain and reflux (Figure 2(b)), compared to non-coeliac 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 2(c)), while there were no differences in GSRS (data not shown). Increased anxiety was also seen in patients with non-coeliac-related co-morbidities such as malignancies, eating disorders and depression, and in smokers, whereas coexisting type 1 diabetes or thyroid disease were not associated with anxiety and it did not correlate with the time from the diagnosis (data not shown).

Discussion

Our main finding was that coeliac 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 follow-up. Whether the benefits of

Table 2. Current sociodemographic and lifestyle characteristics and comorbidities in adult coeliac 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 coeliac society, no. (%)	18 (37.5)	104 (56.5)	0.019
Coeliac 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

[a]Data available for 37 patients only.
[b]Data available for 149 patients only.
[c]First-degree relatives.
[d]For example, other gastrointestinal disease, rheumatic disease, hypertension, cancer, osteoporosis, psoriasis, depression, eating disorder or asthma.
[e]More than three times per week.
IQR: interquartile range; no.: number.

Table 3. Current health experiences, dietary adherence and follow-up in adult coeliac 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 coeliac 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 coeliac disease, no. (%)			0.467
Regular	14 (29.2)	45 (24.1)	
None or occasional	34 (70.8)	142 (75.9)	

[a]Self-assessment.
[b]Perceived as being caused by coeliac disease.
[c]Lapses every week to 1 month.
no.: number.

Table 4. Current characteristics in subgroups of asymptomatic and symptomatic screen-detected coeliac 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
Coeliac disease in the family, no. (%)	22 (81.5)	16 (76.2)	0.729
Coeliac 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 coeliac 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[e]	3 (11.1)	3 (14.3)	
No diet	0 (0.0)	0 (0.0)	
Follow-up of coeliac 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]Perceived as being be caused by coeliac disease.
[e]Lapses every week to 1 month.
IQR: interquartile range; no.: number.

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 asymptomatic screen-detected patients are also at risk of developing 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 coeliac 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 4 years on the diet.[22] Fabiani et al. reported a mere 23% of screen-detected adolescents maintaining a strict diet after 5 years compared to 68% of those found because of malabsorptive symptoms.[15] Besides these paediatric studies, we and Mahadev et al. have observed similar dietary adherence patterns between cohorts of screened and clinically-detected adults, in which some individuals 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 paediatric 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 of the prevailing knowledge of coeliac 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

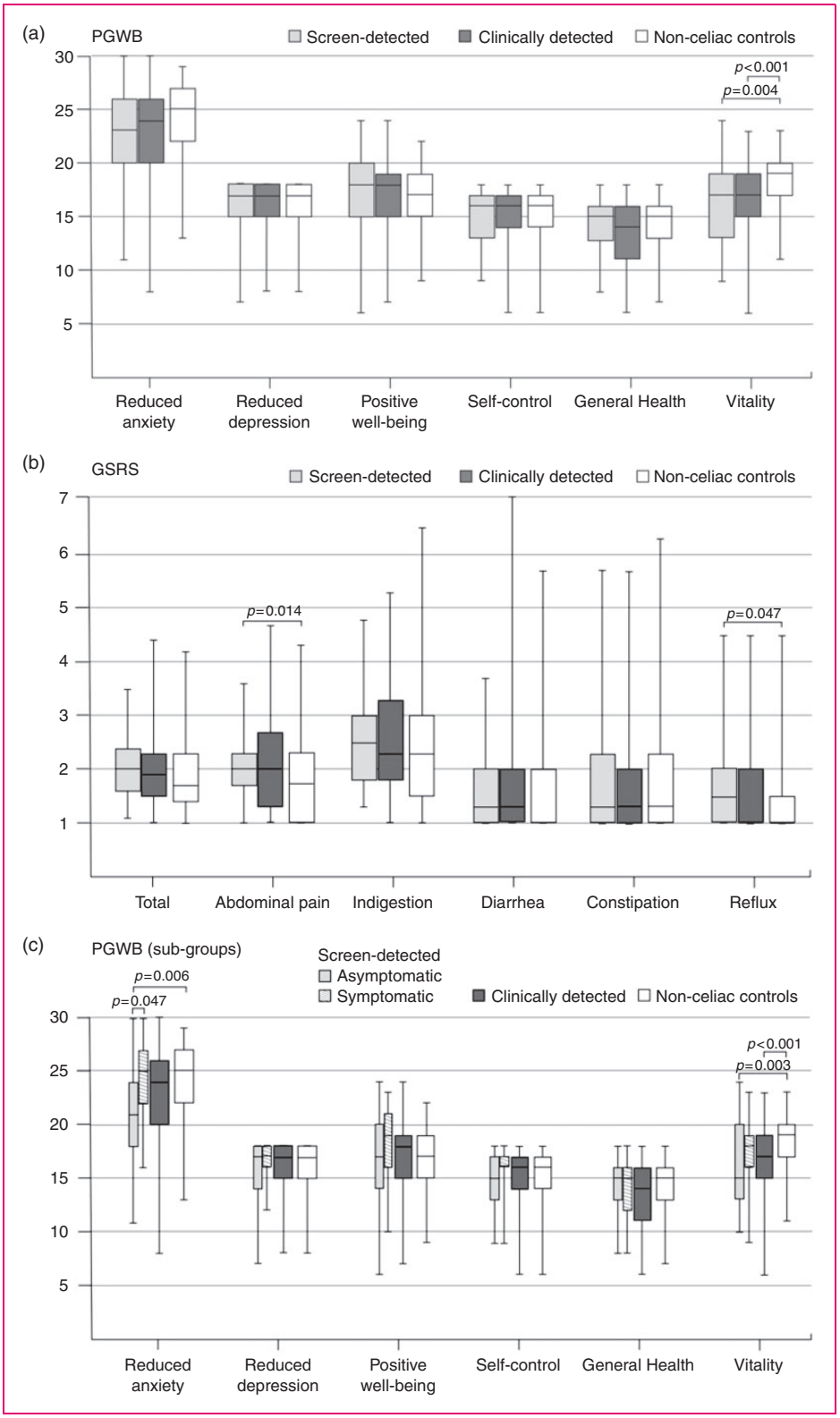

Figure 2. Psychological General Well-Being and Gastrointestinal Symptom Rating Scale subscores in adults.
Coeliac disease patients were first divided into those diagnosed in childhood via risk-group screening ($n = 48$) and due to clinical suspicion ($n = 188$) ((a) and (b)), and the group of screen-detected 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-coeliac adults are shown for comparison. Higher scores indicate either better psychological well-being ((a) and (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), interquartile range (box), and minimum and maximum values (vertical line) of the scores are presented for each patient group.
PGWB: Psychological General Well-Being; GSRS: Gastrointestinal Symptom Rating Scale.

in different populations are needed, but we here demonstrated that, in favorable circumstances, the achievement of 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 that a higher proportion of those with type 1 diabetes were screen-detected compared to those that were clinically found, since these patients are particularly advised to avoid smoking strictly to prevent diabetes-associated long-term complications.

A gluten-free diet is necessary to achieve remission in coeliac disease, but can be challenging in many respects. Here, screen-detected and clinically identified patients did not differ in quality of life or their 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 regarding 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 a gluten-free diet.[14] However, even at that point, these patients were still in early adolescence (<15 years) and the treatment was mainly the parents' responsibility.

Clinical presentation and particularly the absence of symptoms may affect the experience of an individual with coeliac disease even more than the original reason for diagnostic evaluation.[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] However, in practice, the required studies are particularly laborious and may take decades to complete with sufficient power. Our center has a long tradition in coeliac disease research, which has enabled us to obtain a unique cohort of adults diagnosed by childhood screening from as far back as the 1970s.[18,31] Another issue that must be considered when discussing screening is that it is not a synonym for an absence of symptoms, as many of these patients are not asymptomatic but simply unrecognized,[7,10,23] as was 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 already important arguments favoring coeliac disease screening 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 already had signs of anaemia and poor growth, and others have reported that such patients can suffer from osteopaenia 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 accordance 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 coeliac 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 coeliac disease diagnosed in childhood. We also succeeded in collecting comprehensive medical data at diagnosis together with data on a variety of current sociodemographic, health and lifestyle factors. 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 were more likely to answer 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-coeliac controls were older and more often female than coeliac disease patients, which may have affected the comparability of quality of life.[35]

Conclusions

We have provided evidence, which was previously lacking, regarding the long-term health outcomes in

screen-detected coeliac 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 against screening, but encourage physicians to take clinical presentation into account when planning long-term follow-up. At this point, we feel that affected children and their families at least have a right to be aware of the underlying coeliac 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.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Informed consent

Informed consent was obtained from patients participating in earlier interviews or answering the questionnaires.

Ethics approval

The study was approved by Regional Ethics Committee of Tampere University Hospital (Ethical committee code R16091, 31 May 2016).

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