Student thesis

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Endoscopic findings in patients with coeliac disease

Student thesis in Medicine
Supervisor: Eivind Ness-Jensen
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Abstract

Background

Coeliac disease (CD) is a chronic small intestinal immune-mediated enteropathy which occurs in genetically predisposed individuals by exposure to ingested gluten, globally affecting 0.6-1% of the world's population. CD mainly affects the gastrointestinal tract, but may also affect other organs. CD may therefore present with a wide range of symptoms and signs. Diagnosing CD in adults is a multiple-step process, consisting of the medical history and clinical findings, serological- , endoscopic- and histopathological findings.

Aim

The aim of this study was to assess the necessity of performing an endoscopy with biopsy of the small intestine to confirm the diagnosis and the additional yield by diagnosing other conditions, in a general adult population screened for CD.

Methods

This study was based on the fourth Trøndelag health study (HUNT4) and data from medical records at Nord Trøndelag Hospital Trust. Participants with anti-TG2 IgA ≥0.7 mg/L or anti-TG2 IgG ≥1.0 mg/L were considered seropositive and were included in the study. The CD diagnosis was confirmed by Marsh grad 3a or higher. Those with a Marsh grade 0, 1 or 2 were considered potential CD. Journal review was conducted to find additional endoscopic findings among seropositive participants who had undergone diagnostic endoscopic examination. Additional endoscopic findings were categorized and summarized. Multivariable logistic regression analysis reporting odds ratio (OR) and 95% confidence interval (CI) was used to estimate the risk of additional findings for both the seropositive population and the population with confirmed CD. The risk was adjusted for sex, age and use of medications (non-steroid anti-inflammatory drugs [NSAIDs]/acetylsalicylic acid [ASA] and proton pump inhibitors [PPIs]/histamine-2 receptor antagonists [H2RAs]).

Results

Among the 54 541 HUNT4 serologically tested participants, 716 were seropositive and had undergone diagnostic endoscopic examination. Among the 716 participants, 476 (67%) were diagnosed with CD. The remaining 240 (33%) participants were defined as potential CD cases. About 30% of the participants had at least one additional endoscopic finding (excluding

duodenitis). A few premalignant lesions were found (seven Barrett's oesophagus and one adenoma), but only in the population above 50 years of age. There were no malignant findings. The risk of additional endoscopic findings increased with advancing age, with a clear increase among the participants above 50 years of age. The risk of additional endoscopic findings was higher among men compared with women and among NSAIDs/ASA and PPIs/H2RAs users.

Conclusion

This study found that the risk of additional non-coeliac related endoscopic findings at a diagnostic endoscopy for CD is low among individuals below the age of 50. Furthermore, the risk of clinically relevant or premalignant findings was minor, especially in the population below 50 years of age. No malignant lesions were found. Our results imply that a no-endoscopy/no-biopsy approach for the diagnosis of CD in adults will not lead to clinically relevant findings being overlooked in the younger adult population.

Introduction

Background

Coeliac disease (CD) is a chronic small intestinal immune-mediated enteropathy which occurs in genetically predisposed individuals, by exposure to ingested gluten (Ludvigsson et al., 2013). Gluten is a mixture of proteins found in wheat (gliadin and glutenin), rye (secalin) and barley (hordein). The innate and adaptive immune reaction to gluten leads to a chronic inflammatory enteropathy, with characteristic changes in the small intestinal mucosa (Green et al., 2015). Both macroscopic and microscopic changes can be observed, like mucosal inflammation, villous atrophy, and crypt hyperplasia (Al-Toma et al., 2019). Severity of symptoms is found to correlate with length of affected bowel. (Dickson et al., 2006)

Epidemiology

CD is a common disease, globally affecting 0.6-1% of the world's population (Al-Toma et al., 2019). A meta-analysis published in 2018 found a global seroprevalence of 1.4% and a biopsy-prevalence of 0.7%, with a wide range of prevalence between individual countries, from 0.2% to 2.4% (Singh et al., 2022). A study conducted in Tromsø, Norway, from 2007 to 2008 revealed a prevalence of CD at 1.5%, where up to 75% of the participants were undiagnosed before the study (Kvamme et al., 2022). CD can appear in all age-groups, at any point in life. The triggers for developing CD are not fully understood, but in some groups the risk of developing CD is higher. These high-risk groups include first-degree relatives of individuals with CD, patients with type 1 diabetes mellitus or other autoimmune diseases, Downs syndrome, and other associated diseases (Al-Toma et al., 2019).

CD has a strong genetic predisposition. Human immune cells express human leukocyte-antigens (HLA), which is inherited from one's parents (Rubin & Crowe, 2020). HLA molecules are divided in to two classes, HLA class 1 and HLA class 2. HLA class 1 includes HLA A-C, which presents peptides broken down from intracellular proteins to $CD8^+$ T-cells. HLA class 2 includes HLA-DR, -DQ and –DP, which presents peptides broken down from extracellular proteins to $CD4^+$ T-cells (Vartdal, 2022). Virtually all individuals with CD carry HLA-DQ2.5, HLA-DQ2.2 and/or HLA-DQ8. The presence of HLA-DQ2/8 is a necessary component for developing CD, but not sufficient alone (Iversen & Sollid, 2023). A meta-analysis published in 2023 concluded that among the individuals expressing HLA-DQ2/8 alleles, those homozygous for HLA-DQ2 have the highest risk of developing CD.

HLA-DQ2 heterozygous also have an increased risk of developing CD, but not to the same extent. HLA-DQ8 is also found in CD individuals but not with the same strong association to CD development as HLA-DQ2. Unlike HLA-DQ2, only homozygous expression of HLA-DQ8 is found to increase the risk of developing CD (Aboulaghras et al., 2023). Studies from the US show that approximately 35% of the American population carries HLA-DQ2 or HLA-DQ8, but most never develop CD (Lebwohl & Rubio-Tapia, 2021).

Symptomatology

CD mainly affects the gastrointestinal tract, but may also affect other organs. CD may therefore present with a wide range of symptoms and signs (Rubin & Crowe, 2020). The onset and course differ between CD patients, some experience acute and severe symptoms, while others present with a subtle or asymptomatic course (Al-Toma et al., 2019). The presentation of CD can be divided into classical, non-classical and asymptomatic (Lebwohl & Rubio-Tapia, 2021).

The classical presentation of CD includes symptoms caused by malabsorption in the small intestine. Malabsorption leads to chronic diarrhea, weight loss, and failure to thrive in children (Lebwohl & Rubio-Tapia, 2021).

The non-classic presentation, which is the most common presentation of CD, includes constipation, bloating, fatigue, and other signs of malabsorption like lack of essential nutrients (iron, fat-soluble vitamins, vitamin B12, and folic acid) resulting in anemia, osteopenia/osteoporosis, and possible neurological manifestations (Lebwohl et al., 2018) (Al-Toma et al., 2019). CD patients can also present with delayed puberty, abnormal lever enzyme levels, and infertility (Lebwohl & Rubio-Tapia, 2021). CD may also give rise to mucocutaneous manifestations like atrophic glossitis and dermatitis herpetiformis (DH) (Schuppan & Dieterich, 2020).

The asymptomatic CD patients are detected due to screening for CD or case finding in high-risk individuals (Lebwohl & Rubio-Tapia, 2021).

Pathogenesis

When gluten is ingested and reaches the small intestine, gluten peptides are transported through the epithelium and into lamina propria, either through the paracellular route or through the transcellular route (Di Sabatino et al., 2012). Transport through the paracellular route is a result of impaired intestinal barrier function due to altered intercellular tight junctions. The gluten peptides bind to chemokine receptor CXCR3 expressed in the intestinal epithelium, leading to MyD88-induced release of zonulin. Zonulin regulates the tight junctions, and the release results in increased epithelial permeability (Lammers et al., 2008). The transcellular route is dependent on retrograde transport of secretory IgA (SIgA). SIgA is produced by plasma cells in lamina propria, and transported to the mucosal lumen by the polymeric immunoglobulin receptor present on the basolateral side of epithelial cells (Breedveld & van Egmond, 2019). Retrograde transport of SIgA immune complexes via the transferrin receptor CD71 mediates transport of intact IgA-bound gluten peptides into lamina propria (Gujral et al., 2012; Matysiak-Budnik et al., 2008).

Tissue transglutaminase (TG) has proven to be of great importance in the pathogenesis of CD (Gujral et al., 2012). It is both a target for antibodies specific for the disease and enchases the immune reaction towards gluten by deamination of gliadin (Di Sabatino et al., 2012). Deamination converts gliadin into glutamic acid, which has a negatively charged side chain in physiological conditions. Areas of the HLA-DQ2/DQ8 antigen-binding groove binds stronger to negatively charged molecules, resulting in a much higher affinity towards gliadin than prior to the deamination (Gujral et al., 2012).

When gliadin has been recognized by HLA-DQ2/DQ8 of antigen precenting cells (APC), it is presented to $CD4^+$ T-cells in a HLA-DQ2/DQ8 antigen complex (Gujral et al., 2012). This stimulates the T-cells to start the immunological response, producing pro-inflammatory cytokines (Di Sabatino et al., 2012) which induce epithelial damage by several mechanisms; (1) by stimulating release of matrix metalloproteinases from fibroblasts and lamina propria mononuclear cells (Di Sabatino et al., 2012) which hydrolyzes and degrades proteins of the extracellular matrix, including the basal membrane (Visse & Nagase, 2003); (2) induce apoptotic death of enterocytes by promoting natural killer cells and intraepithelial lymphocytes (Dickson et al., 2006; Gujral et al., 2012); and (3) induce B-cell expansion and differentiation into plasma cells which produces anti-gliadin and anti-TG antibodies(Di

Sabatino et al., 2012). The epithelial damage caused by these mechanisms give rise to typical celiac lesions with both macroscopic and microscopic changes (Gujral et al., 2012).

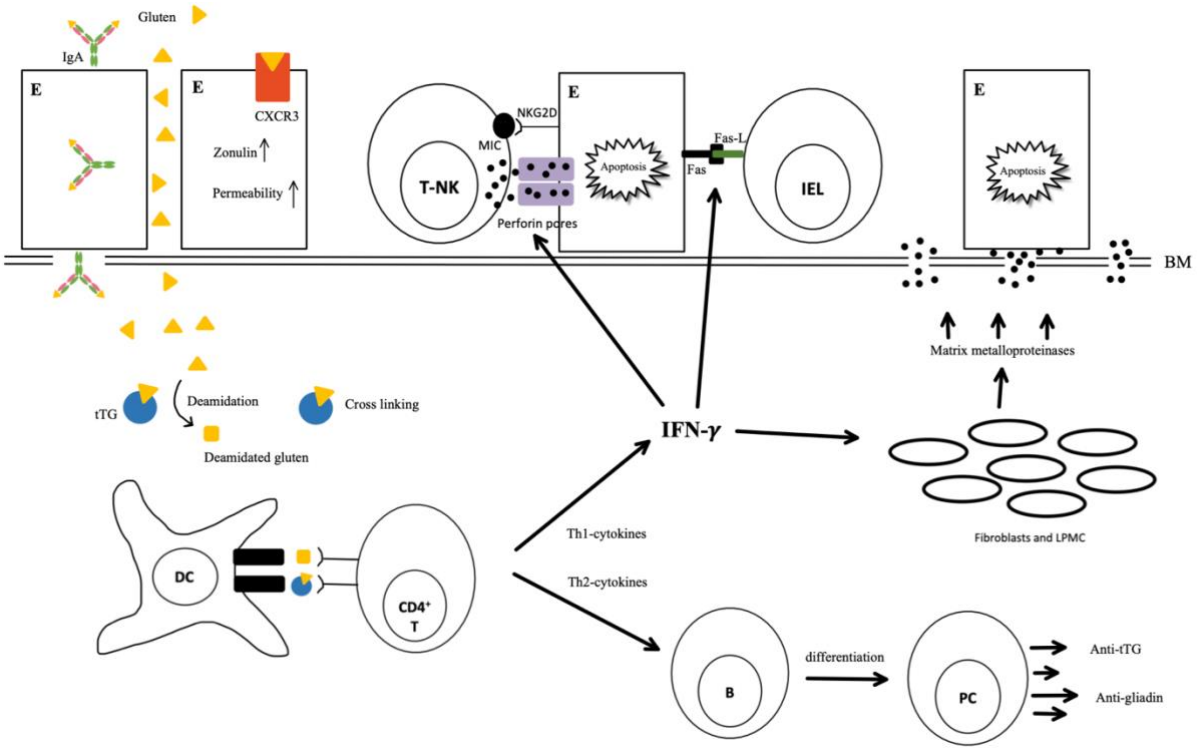


Figure 1 (Di Sabatino et al., 2012). Gliadin absorption via paracellular/transcellular route. Deamidation via tTG. Antigen binding and presentation by APC to T-cells. T-cells produce proinflammatory cytokines, both promoting cytotoxicity of IEL's and NK-cells and inducing B-cell expansion and differentiation. Plasma cells producing anti-tTG and anti-gliadin antibodies. Abbreviations: E, epithelial cell; Ig, immunoglobin; CXCR3, CXC motif chemokine receptor 3; NK, natural killer cell; IEL, intraepithelial lymphocytes; BM, basal membrane; TG, tissue transglutaminase; IFN, interferon ;DC, dendritic cell; T, T-cell; B, B-cell ; PC, plasmacell; LPMC, intestinal lamina propria mononuclear cells.

Diagnostics

Diagnosing CD in adults is a multiple-step process, consisting of the medical history and clinical, serological-, endoscopic-, and histopathological findings (Al-Toma et al., 2019).

The first step in diagnosing CD is to consider the patients report of symptoms and findings from a physical exam (Brown et al., 2012). CD mainly affect the small intestine, but it may also affect other organ systems. Therefore, it may present with a specter of symptoms and signs (Rubin & Crowe, 2020).

The next step is serological testing, developed to detect specific antibodies in blood samples. Several serological tests have been developed to detect CD, based on IgM, IgA and IgG antibodies (Al-Toma et al., 2019). The most used tests detect IgA antibodies against TG2

and IgG antibodies against deamidated gluten peptides (DGP), both specific for CD (Iversen & Sollid, 2023). Anti-TG2 IgA is the first-line serological test used to diagnose CD, and has a 95% sensitivity and specificity for undiagnosed CD in patients on a gluten-containing diet (Lebwohl & Rubio-Tapia, 2021). Some patients produce low or no IgA antibodies, causing a false negative result. Measuring total IgA along with the serological test determine if the patient produces sufficient levels of IgA. IgA deficiency appears in 2-3% of CD patients (Al-Toma et al., 2019), and in these patients the diagnosis can be assessed using anti-DGP IgG or anti-TG2 IgG (Lebwohl & Rubio-Tapia, 2021).

In children, the diagnosis can be confirmed if there are symptoms or signs suggesting CD and the anti-TG2 IgA is above 10 times the upper limit of normal in two separate blood tests and a positive EMA blood test (Husby et al., 2020). In adults, the diagnosis needs to be confirmed with an upper endoscopy and biopsy while still on a gluten containing diet (Al-Toma et al., 2019). Macroscopic findings during endoscopy strengthens the suspicion but are not always present. Microscopic findings in biopsies collected from the duodenum are diagnostic for CD (Lebwohl et al., 2018). Some studies have discussed a biopsy avoidance diagnosis strategy in adults as well as in children (Maimaris et al., 2020; Mott et al., 2022; Stefanolo et al., 2022).While others express the danger of overlooking important findings of additional illnesses and associated conditions if the diagnosis is to be made without endoscopic confirmed diagnosis and biopsies (Al-Toma et al., 2019).

Morphology

Typical signs of CD at endoscopy are atrophy and visible submucosal vessels, fissures and reduction of circular folds (Al-Toma et al., 2019). In most cases the severity of morphological changes decreases distally (Dickson et al., 2006). Histologically, one may find architectural changes (e.g., villous atrophy, crypt hyperplasia, thickened basal membrane, fewer goblet cells), signs of inflammation (e.g., increased number of IELs, immune cells in lamina propria) and enterocyte changes (e.g., cuboidal morphology, loss of typical basal nuclei, cytoplasmic vacuoles) (Dickson et al., 2006).

For the biopsies to be reliable, they should include three to four following villous-crypt units arranged parallel to each other (Al-Toma et al., 2019). Four biopsies from the horizontal part of the duodenum and two from the bulb are recommended. The histological assessment includes crypt depth and villous height measurements, number and distribution

pattern of intraepithelial lymphocytes (IELs) and a conclusion according to the Marsh-Oberhuber stages of CD (Al-Toma et al., 2019).

Marsh proposed a grading of the histopathological changes in CD through four stages (Table 1). Thereafter, a new standardized reporting system based on the Marsh classification was proposed by Oberhuber et al., where stage 3 was split further into 3A, 3B and 3C differentiated by mild, marked and completely flat mucosa (Table 2). (Corazza & Villanacci, 2005). Today, >25 IEL/100 enterocytes are considered pathological (Al-Toma et al., 2019).

Table 1: Characteristics of Marsh stages of celiac disease, based on observations in duodenal biopsies (Corazza & Villanacci, 2005).

STAGE	LESION TYPE	CHARACTERISTICS
STAGE 1	Infiltrative lesions	Normal architecture with an increased number of intraepithelial lymphocytes
STAGE 2	Hyperplastic lesions	Increase in crypt depth (crypt hypertrophy) without villous flattening
STAGE 3	Destructive lesions	Villous atrophy and crypt hypertrophy
STAGE 4	Hypoplastic lesions	Villous atrophy with normal crypt height and intraepithelial lymphocytes count

Table 2: Criteria for Marsh-Oberhuber stages of celiac disease, based on observations in duodenal biopsies (Brown et al., 2012).

	STAGE 1	STAGE 2	STAGE 3A	STAGE 3B	STAGE 3C	STAGE 4
IEL COUNT	> 40	> 40	> 40	> 40	> 40	> 40
CRYPTS	Normal	Hypertrophic	Hypertrophic	Hypertrophic	Hypertrophic	Atrophic
VILLI	Normal	Normal	Mild atrophy	Marked atrophy	Absent	Absent

Abbreviations: IEL, intraepithelial lymphocyte

Treatment

To stop the inflammatory reaction and reverse the damage to the small intestinal mucosa, the patient needs to stay on a strict gluten-free diet (GFD) (Al-Toma et al., 2019). GFD is the only approved treatment for CD per date. A GFD will lead to normalization of the intestinal mucosa and decreasing/normalization of antibodies in the patient's blood (Al-Toma et al., 2019).

Aim

The standard diagnostic procedure today differs between children and adults. In children the diagnosis can be confirmed with repeated serological testing, while in adults the diagnosis must be confirmed with endoscopy and biopsy of the small intestine. One advantage with endoscopy and biopsy confirmation of the diagnosis is the possibility to look for other conditions, such as esophagitis, gastritis, duodenitis, ulcers, cancer, and other conditions located in the esophagus, stomach or duodenum. However, endoscopic examinations are expensive and resource demanding, and may cause complications or be considered a strain for the patient.

The aim of this study was to assess the necessity of performing an endoscopy with biopsy of the small intestine to confirm the diagnosis and the additional yield by diagnosing other conditions, in a general adult population screened for CD.

Materials and methods

Study population

This study was based on the fourth Trøndelag health study (HUNT4). HUNT consists of a series of population-based surveys conducted in the former Nord-Trøndelag county, Norway. All adult inhabitants, aged 20 years or older, were invited to participate in the study (Krokstad et al., 2013). Four HUNT-studies have been conducted since 1984; HUNT1 (1984-1986), HUNT2 (1995-1997), HUNT3 (2006-2008), and HUNT4 (2017-2019). The HUNT-surveys included questionnaires, interviews, clinical examinations, anthropometric measurements and laboratory measurements from blood samples. In addition, biological samples (blood, urine, saliva, and feces) were collected and stored at HUNTs Biobank (Asvold et al., 2023). Questionnaires including anamnestic key points such as socioeconomic conditions, health related behaviors, symptoms, illnesses, and diseases were also included. The collected data is linked to each participant's unique Norwegian personal identification number, making it possible to link the participants HUNT-data to their hospital records at the local hospital of the HUNT population, Nord-Trøndelag Hospital Trust (Levanger and Namsos hospitals) and the regional university hospital, St. Olav's Hospital (Asvold et al., 2023).

Study design

In HUNT4, 54541 participants donated blood for analysis and storage in HUNTs biobank. Serum from all participants in HUNT4 was analyzed for anti-TG2 (IgA and IgG) at Oslo University Hospital. Participants with anti-TG2 IgA ≥0.7 mg/L or anti-TG2 IgG ≥1.0 mg/L were considered seropositive. All the seropositive participants were invited to clinical assessment and validation of the serological result at Levanger Hospital. The participants received a personal invitation letter to the study, including information about the study and the endoscopic procedure, a written informed consent, and an appointment letter.

The clinical assessment involved new serological tests (both anti-TG2 IgA and anti-DGP IgG) and upper endoscopy with small intestinal single bite biopsies from pars horisontalis (n=4) and bulb (n=2).

The endoscopic examinations were performed by experienced endoscopists, and the findings were reported in a standardized format. The biopsies taken during endoscopy were fixated on formalin containing tubes and sent to Department of Pathology at St. Olav's

Hospital. Histological and immunohistochemical examination with CD3 staining were performed on the biopsies. The CD diagnosis was confirmed by Marsh grad 3a or higher, after exclusion of other possible explanations of the duodenal changes, including Helicobacter pylori infection (by PCR of stomach biopsies) and NSAIDs or ASA use. Those with a Marsh grade 0, 1 or 2 were considered potential CD patients and were recommended to continue a gluten-containing diet followed by a new diagnostic procedure at least one year later. All seropositive participants, both confirmed and potential CD patients, were invited to a one-year follow-up.

Data collection

In the present study, information on the following variables was collected from HUNT: sex, age, use of medications (NSAIDs, ASA, PPIs and H2RA), CD-serology titre, histological findings, and diagnostic conclusions. In addition, there was conducted a systematic search of the diagnostic endoscopy reports from Nord-Trøndelag Hospital Trust in all seropositive HUNT4-participants. Endoscopic reports from patients with positive serological test in HUNT4 who had undergone endoscopic examination outside the HUNT4 study were also included in the review. The aim was to detect additional endoscopic findings at the diagnostic endoscopy in seropositive patients. The systematic search was done manually by two collectors and reviewed by the two collectors and an experienced gastroenterologist.

Additional findings at the upper endoscopy among the seropositives were described with 15 different ICD-codes (Table 3). Duodenitis was defined as red spots or erosions in bulb/duodenum. Because duodenitis is an expected observation among patients with CD, it was decided to exclude these findings from the risk analyses. Gastroduodenitis was included because gastritis is not a typical expected finding in CD affecting the horizontal and bulbar parts of duodenum. Among the patients with biopsy confirmed Barrett's esophagus, 6 had confirmed intestinal metaplasia and 1 had only gastric metaplasia.

Table 3: Overview of reported findings from the diagnostic endoscopy of the seropositive HUNT4 population	
ICD10_diagnosis	**ICD10_code**
Duodenal adenoma	D13.2
GERD with esophagitis	K21.0
GERD without esophagitis	K21.9
Esophageal-stricture	K22.2
Barrett's esophagus (biopsy confirmed)	K22.7
Ventricular ulcer	K25
Duodenal ulcer	K26
Gastritis	K29
Cameron-lesion	K29.6
Duodenitis	K29.8
Gastroduodenitis	K29.9
Fundic gland polyp	K31.7
GAVE	K31.8
Unspecified disease of stomach and duodenum	K31.9
Hiatal hernia	K44.9

Abbreviations: HUNT, Trøndelag Health Study; GERD, gastroesophageal reflux disease; GAVE, Gastric antral vascular ectasia

Data analyses

The number of additional endoscopic findings among the seropositives and among those with confirmed CD was summarized, respectively. The endoscopic findings were stratified by sex and age groups with 10-year intervals. Multivariable logistic regression analyses were used to estimate the risk of additional endoscopic findings adjusted for sex, age, and use of NSAIDs/ASA and PPIs/H2RAs. All statistical analyses were performed using STATA (STATA version 17.0 Corp, College Station, TX, United States).

Study approval

The study was approved by the Regional Committee for Medical and Health Research Ethics Central (#7943) and by HUNT Research Center (#2022/17790). All participants gave an informed written consent when they participated in the HUNT4 study and before the endoscopy. The journal review was approved by Nord-Trøndelag Hospital Trust (#2022_2435).

Results

Characteristics of the study population

Among the 54,541 HUNT4 participants with serum samples screened for CD, 1047 were found to be seropositive (Figure 2). Of these, 716 had diagnostic endoscopy with duodenal biopsies performed and were included in the present study. Of the 716 included participants, 476 (67%) were diagnosed with CD. The remaining 240 (33%) participants without CD were defined as potential CD cases.

Among both the seropositives and the participants with confirmed CD there were more women (54%) than men (Table 4). The median age of the seropositives was 57 years, ranging from 16 to 91 years. The median age of the confirmed CD population was 55 years ranging from 16 to 87 years. Of the seropositives, 275 (38%) participants were below the age of 50, and of these 195 (71%) were diagnosed with CD. 51 participants in the population had known CD from before inclusion in the project. Of the seropositives, 203 (28%) reported using NSAIDs or ASA and 81 (11%) reported using PPIs or H2RAs.

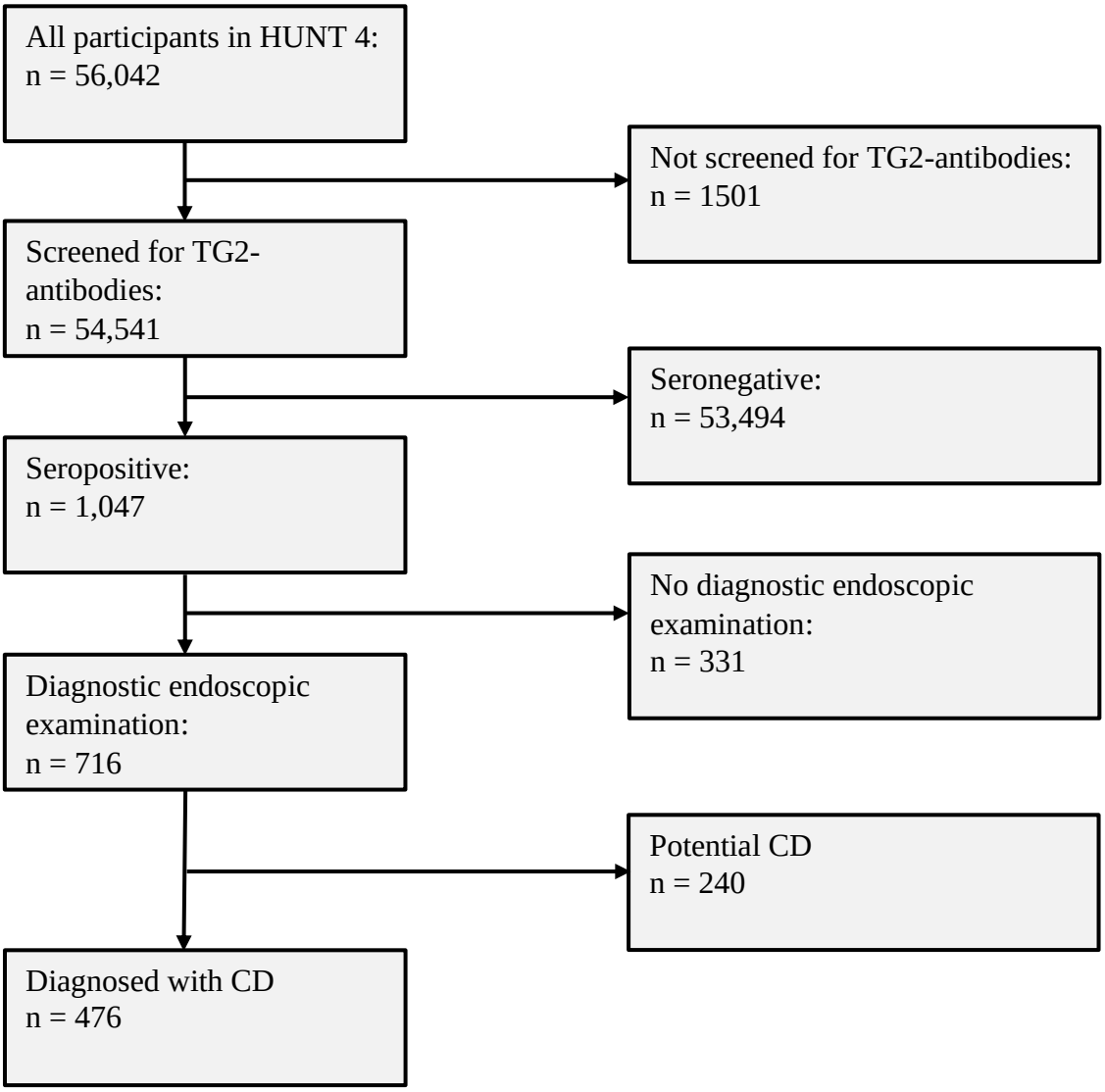


Figure 2: Flowchart of the participants included in the study. Cut-off values of antibody titer for seropositives were set at TG2-IgA ≥ 0.7 mg/L or TG2-IgG ≥ 1.0 mg/L if TG2-IgA < 0.7 mg/L. Abbreviations: CD, coeliac disease; HUNT, Trøndelag Health Study; Ig, immunoglobulin; TG, transglutaminase.

Table 4: Characteristics of the seropositive HUNT4 population		
	Total population (potentials and confirmed)	**Confirmed coeliac disease**
	716	476 (66.5)
Women, number (%)	387 (54.1)	260 (54.6)
Men, number (%)	329 (45.9)	216 (45.4)
Age in years		
Mean (SD)	54.8 (16.1)	53.3 (16.3)
Median	57	55
Range	16-91	16-87
Age groups in years, number (%)		
<=30	73 (10.2)	58 (12.2)
31-40	75 (10.5)	52 (10.9)
41-50	126 (17.6)	85 (17.9)
51-60	141 (19.7)	102 (21.4)
61-70	177 (24.7)	105 (22.1)
71-80	107 (14.9)	65 (13.7)
>80	17 (2.4)	9 (1.9)
Use of NSAIDs/ASA, number (%)	203 (28.4)	124 (26.1)
Use of PPIs/H2RAs, number (%)	81 (11.3)	40 (8.4)
At least one additional endoscopic finding (including duodenitis), number (%)	505 (70.5)	343 (72.1)
At least one additional endoscopic finding (excluding duodenitis), number (%)	233 (32.5)	140 (29.4)

Abbreviations: HUNT, Trøndelag Health Study; SD, standard deviation; NSAID, non-steroidal anti-inflammatory drugs; ASA, acetylsalicylic acid; PPIs, proton pump inhibitors; H2RAs, histamine 2 receptor antagonists.

Additional endoscopic findings

The review of the endoscopic reports resulted in at least one additional (non-coeliac related) endoscopic finding in 233 (33%) of the seropositives, and in 140 (29%) of those with confirmed CD (Table 4).

The most common finding among the seropositives was duodenitis, found in 342 (48%) participants, followed by hiatal hernia in 107 (15%), gastroduodenitis in 73 (10%) and reflux esophagitis in 57 (8%). Seven (0.1%) participants had Barrett's esophagus, 3 (0.4%) had duodenal ulcers, 2 (0.3%) had ventricular ulcers and one had a duodenal adenoma (0.1%) (Table 5). The percentage of participants with additional findings increased with advancing age, with a clear distinction in percentage of participants with at least one additional endoscopic findings in age groups below 50 years of age (<17%) and those above 50 years of age (>29%) (Table 5).

The additional findings in those with confirmed CD did not differ significantly from the whole seropositive population, except that only one pre-cancerous lesion (Barrett’s esophagus) and one duodenal ulcer was reported in the upper endoscopic examinations performed on participants with confirmed CD (Table 6).

Among the 233 seropositives with at least one additional endoscopic finding, 113 were women and 120 were men, showing an increased prevalence of additional endoscopic findings in men (37%) compared with women (29%) (Table 7). A similar relationship was seen among those with confirmed CD (Table 8).

Table 5: Additional (non-coeliac related) endoscopic findings in all seropositive participants in HUNT4, by age groups

Diagnosis	<=30	31-40	41-50	51-60	61-70	71-80	Age>80	Sum
At least one additional endoscopic finding (excluding duodenitis)	9 (12.3%)	13 (17.3%)	22 (17.5%)	41 (29.1%)	78 (44.1%)	57 (53.3%)	13 (76.5%)	233 (32.5%)
No findings	64	62	104	100	99	50	4	483
Sum	73	75	126	141	177	107	17	716
Adenoma in duodenum (D13.2)	0	0	0	0	0	1	0	1 (0.1%)
GERD with esophagitis (K21.0)	2	2	6	17	19	10	1	57 (7.9%)
GERD without esophagitis (K21.9)	0	0	0	0	3	2	1	6 (0.8%)
Esophageal-stricture (K22.2)	0	0	0	0	0	1	0	1 (0.1%)
Barrett's esophagus (biopsy confirmed) (K22.7)	0	0	0	2	2	3	0	7 (0.97%)
Ventricular ulcer (K25)	0	0	0	0	2	0	0	2 (0.3%)
Duodenal ulcer (26)	0	0	0	1	1	0	1	3 (0.4%)
Gastritis (K29)	1	3	4	7	17	6	3	41 (5.7%)
Cameron-lesion (K29.6)	0	0	0	0	0	1	0	1 (0.1%)
Duodenitis (K29.8)	34	31	66	75	80	51	5	342 (47.8%)
Gastroduodenitis (K29.9)	5	5	7	6	28	19	3	73 (10.2%)

Fundic gland polyps (K31.7)	2	1	5	7	10	7	1	33 (4.6%)
GAVE (K31.8)	0	0	0	0	0	1	0	1 (0.1%)
Unspecified disease of stomach and duodenum (K31.9)	0	0	1	0	1	0	0	2 (0.3%)
Hiatal hernia (K44.9)	2	5	6	18	32	36	8	107 (14.9%)
Total findings (excluding duodenitis)								335
Total findings								677

Abbreviations: HUNT, Trøndelag Health Study; GERD, gastroesophageal reflux disease; GAVE, gastric antral vascular ectasia

Table 6: Additional (non-coeliac related) endoscopic findings in participants with confirmed coeliac disease in HUNT4, by age groups

Diagnosis	<=30	31-40	41-50	51-60	61-70	71-80	Age>80	Sum
At least one additional endoscopic finding (excluding duodenitis)	8 (13,8%)	9 (17,3%)	13 (15,3%)	31 (30,4%)	42 (40,0%)	31 (49,2%)	6 (66,7%)	140 (29,4%)
No findings	50	43	72	71	63	34	3	336
Sum	58	52	85	102	105	65	9	476
Duodenal adenoma (D13.2)	0	0	0	0	0	0	0	0
GERD with esophagitis (K21.0)	2	2	3	12	8	7	0	34 (7,1%)
GERD without esophagitis (K21.9)	0	0	0	0	1	1	0	2 (0,4%)
Esophageal-stricture (K22.2)	0	0	0	0	0	0	0	0
Barrett's esophagus (biopsy confirmed)(K22.7)	0	0	0	0	1	0	0	1 (0,2%)
Ventricular ulcer (K25)	0	0	0	0	0	0	0	0
Duodenal ulcer (K26)	0	0	0	1	0	0	0	1 (0,2%)
Gastritis (K29)	1	2	1	6	8	3	2	23 (4,8%)
Cameron-lesion (K29.6)	0	0	0	0	0	0	0	0
Duodenitis (K29.8)	29	23	51	60	53	33	2	251 (52,7%)
Gastroduodenitis (K29.9)	5	4	6	5	18	9	2	49 (10,3%)
Fundic gland polyps (K31.7)	1	1	3	3	7	4	0	19 (4%)

GAVE (K31.8)	0	0	0	0	0	1	0	1 (0,2%)
Unspecified disease of stomach and duodenum (K31.9)	0	0	1	0	1	0	0	2 (0,4%)
Hiatushernia (K44.9)	1	3	3	14	17	21	4	63 (13,2)
Total findings (excluding duodenitis)								195
Total findings								446

Abbreviations: HUNT, Trøndelag Health Study; GERD, gastroesophageal reflux disease; GAVE, Gastric antral vascular ectasia

Table 7: Additional (non-coeliac related) endoscopic findings in all seropositive participants in HUNT4, by sex

	Men	Women	Sum
At least one endoscopic finding	120 (36.5%)	113 (29.2%)	233 (32.5%)
No findings	209	274	483
Sum	329	387	716

Abbreviations: HUNT, Trøndelag Health Study

Table 8: Additional (non-coeliac related) endoscopic findings in patients with confirmed coeliac disease in HUNT4, by sex

	Men	Women	Sum
At least one endoscopic finding	69 (31.9%)	71 (27.3%)	140 (29.4%)
No findings	147	189	336
Sum	216	260	476

Abbreviations: HUNT, Trøndelag Health Study

The risk of additional endoscopic findings in seropositives and confirmed CD.

The multivariable analysis in the seropositives showed an increased risk of additional endoscopic findings with advancing age, with a clear distinction between those above and below 50 years of age. The highest risk was found among the seropositive participants >80 years of age (adjusted OR 21.3, 95% CI 5.6-80.6). The use of PPIs/H2RAs also increased the risk of additional endoscopic findings (adjusted OR 2.4, 95% CI 1.4-3.9) (Table 9). Similar risks were also found among the participants with confirmed CD (Table 10).

Table 9: The risk of additional (non-coeliac related) endoscopic findings in seropositive participants in HUNT4

Variable	At least one endoscopic lesion (excluding duodenitis)			
	Crude		Adjusted*	
	OR	95% CI	OR	95% CI
Male sex	1.4	1.0-1.9	1.2	0.9-1.7
Age, 1 year increase in age	1.0	1.0-1.1	1.0	1.0-1.1
Age <=30 (ref)				
Age 31-40	1.5	0.6-3.7	1.5	0.6-3.8
Age 41-50	1.5	0.6-3.5	1.4	0.6-3.3
Age 51-60	2.9	1.3-6.4	2.9	1.3-6.5
Age 61-70	5.6	2.6-12.0	5.1	2.4-10.9
Age 71-80	8.1	3.7-17.9	7.1	3.2-15.9
Age >80	23.1	6.2-86.5	21.3	5.6-80.6
NSAIDs/ASA	1.4	1.0-2.0	1.1	0.8-1.7
PPI/H2RA	3.0	1.9-4.8	2.4	1.4-3.9

Abbreviations: HUNT, Trøndelag Health Study; OR, odds ratio; CI, confidence interval; NSAID, Non-Steroidal Anti-Inflammatory Drugs; ASA, acetylsalicylic acid; PPI, proton pump inhibitor; H2RA, Histamine 2 receptor antagonists.

** Sex, age with 1 year interval, NSAIDs/ASA and PPI/H2RA adjusted for each other. Age categories analysed in separate analysis, adjusted for sex, NSAIDs/ASA and PPI/H2RA. Reference values: women, age <= 30, no use of NSAIDs/ASA, no use of PPIs/H2RAs.*

Table 10: The risk of additional (non-coeliac related) endoscopic findings in participants with confirmed coeliac disease in HUNT4

Variable	At least one endoscopic lesion (excluding duodenitis)			
	Crude		Adjusted*	
	OR	95% CI	OR	95% CI
Male sex	1.2	0.8-1.9	1.1	0.7-1.7
Age, 1 year increase in age	1.0	1.0-1.1	1.0	1.0-1.1
Age <=30 (ref)				
Age 31-40	1.3	0.5-3.7	1.4	0.5-3.9
Age 41-50	1.1	0.4-2.9	1.1	0.4-2.9
Age 51-60	2.7	1.2-6.4	2.8	1.2-6.7
Age 61-70	4.2	1.8-9.7	3.8	1.6-9.0
Age 71-80	5.7	2.3-13.9	5.1	2.1-12.6
Age >80	12.5	2.6-60.3	11.7	2.4-57.7
NSAIDs/ASA	1.3	0.8-2.0	1.1	0.7-1.8
PPIs/H2RAs	3.3	1.7-6.4	2.5	1.2-5.0

Abbreviations: HUNT, Trøndelag Health Study; OR, odds ratio; CI, confidence interval; NSAID, Non-Steroidal Anti-Inflammatory Drugs; ASA, acetylsalicylic acid; PPI, proton pump inhibitor; H2RA, Histamine 2 receptor antagonists.

** Sex, age with 1 year interval, NSAIDs/ASA and PPI/H2RA adjusted for each other. Age categories analysed in separate analysis, adjusted for sex, NSAIDs/ASA and PPI/H2RA. Reference values: women, age <= 30, no use of NSAIDs/ASA, no use of PPIs/H2RAs.*

Discussion

Main findings

In this population-based study of seropositives and biopsy confirmed CD participants, there was a low rate of clinically relevant additional endoscopic findings and no malignant findings. A few premalignant lesions were found, but only in the population above 50 years of age and the risk of additional findings increased with advancing age. Use of PPIs/H2RAs increased the risk of additional endoscopic findings.

Comparison with existing research

A multicenter retrospective study from Italy, Canada and Argentina published in 2022, with participants included from 1987-2021, reported no concomitant endoscopic findings in 92% of their 1328 study participants (Stefanolo et al., 2022). This was considerably lower than in the present study, but could be explained by fewer ICD-codes included in their data collection. Similar to the present study, the multicenter study also had low occurrence of more severe endoscopic findings (e.g., peptic ulcer disease and Barrett's esophagus), and reported low prevalence of additional findings among the younger population and increasing occurrence with increasing age >50 years. This was a large multicenter study, but their data were collected retrospectively and the possibility of underestimated prevalence due to lack of systematic collection across the different centers was discussed.

Another retrospective study from Italy published in 2020 looked at the occurrence of additional endoscopic findings in endoscopic reports of 278 biopsy confirmed CD patients (Maimaris et al., 2020). The study included participants diagnosed with CD from 1999 to 2017. In the study, 14.4% of the participants had additional findings on the diagnostic endoscopy. No malignancies, pre-malignancies or ulcers were found.

No previous study has investigated the risk of additional endoscopic findings in relation to the use of medications at the diagnostic investigation in CD patients. The present study found an increased risk of additional endoscopic findings with use of PPIs/H2RAs. The main indication for these medications are symptoms of GERD, which increases the risk of finding macroscopic changes upon upper endoscopy. Moreover, the use of PPIs/H2RAs is higher among the older population who already have an increased risk of additional endoscopic findings due to their age.

Ethical considerations regarding a no-biopsy approach for diagnosis in adults

When screening the general population for CD, the risk of false positive serological findings will increase, compared to examining symptomatic patients (Mearin et al., 2005). This will lead to unnecessary endoscopic procedures that may cause patients to feel anxiety or discomfort, and represent an avoidable economical expense and use of resources. Performing an upper endoscopy with biopsy on a false positive also exposes the patient to possible complications (e.g., pain, bleeding, infections and perforation) (Eisen et al., 2002) (Merchea et al., 2010). Patients also risk having a reaction to the sedatives given to some patients prior to the endoscopy. Reactions vary from effected vital signs to severe complications such as myocardial infarction, respiratory depression and shock (Eisen et al., 2002). However, these complications are very rare. Furthermore, screening may also lead to overdiagnosing of CD (Green & Guandalini, 2019). These individuals may never develop symptoms or complications related to CD, and are advised to live by a gluten free diet unnecessary, which may affect quality of life and cause inadequate nutrition. On the other hand, early diagnosis reduce the risk of villous atrophy and associated complications such as intestinal adenocarcinoma and lymphoma. However, more recent studies show lower risk of these complication than previously reported (Mearin et al., 2005).

Strengths and limitations

A strength of this study is the population-based design which include all adult seropositive participants in a general population, also those previously undiagnosed. The HUNT4 study had a large sample size and high participation rate for a population-based study, resulting in a study population consisting of participants with a wide age span representing different professions and different economic and social background. The examinations were conducted by two experienced gastroenterologists, and the findings were reported in a pre-developed form. By using the participants' unique personal identification number, linkage between the HUNT study and the individual participant's hospital records was possible to validate the endoscopic findings.

A limitation is that the journal review was conducted by two medical students who had limited experience in the field. However, they performed the collection and interpretation of information from mainly standardized endoscopic reports, and their review was overseen and discussed with an experienced gastroenterologist. The involvement of the gastroenterologist ensures that the interpretation of the data is accurate and reliable. Although

the majority of the endoscopic examinations were performed by the two gastroenterologists from the HUNT study, some examinations performed by others on participants with pre-existing CD were included. In these cases, the endoscopic reports were not pre-defined and lacked the same systematic organization. Consequently, the interpretation of the reported findings from these examinations are more uncertain. However, for most reports the information can still be considered reliable, as most of the examinations were conducted by trained gastroenterologists.

Consequences for future diagnostics

The current guidelines argue that a no-endoscopy/no-biopsy approach could endanger the patients by the risk of overlooking potentially dangerous lesions and associated diseases (Al-Toma et al., 2019). However, in the present study only 1/3 of the endoscopies had additional findings, and the risk of potentially dangerous lesions was very low. The study also found that the risk of additional (non-coeliac related) endoscopic findings mainly was found in the older individuals (above 50 years of age). With these findings it can be argued that a no-endoscopy/no-biopsy approach can be considered in the younger adult individuals with possible CD (below 50 years of age). Other studies also support our findings and conclusion (Maimaris et al., 2020; Stefanolo et al., 2022).

Despite the large study population, the number of people diagnosed with CD was limited. In addition, a limited number of similar studies have been performed. In order to reach a more reliable conclusion, similar studies should be performed in other large and unselected populations. We have included several risk factors that may affect the outcome of an endoscopic examination, but future investigations could include more risk factors, such as comorbidities and different serological titer cut-offs. This might make it possible to give a more precise answer as to who should benefit from an endoscopy, and who could be diagnosed by serological tests only.

Conclusion

In conclusion, this study found that the risk of additional non-coeliac related endoscopic findings at the diagnostic endoscopy for CD is low among patients below the age of 50. Furthermore, the risk of clinically relevant or premalignant findings was minor, and no malignant lesions were found. Our results imply that a no-endoscopy/no-biopsy approach for

the diagnosis of CD will not lead to clinically relevant findings being overlooked in the younger adult population.

References

Aboulaghras, S., Piancatelli, D., Taghzouti, K., Balahbib, A., Alshahrani, M. M., Al Awadh, A. A., Goh, K. W., Ming, L. C., Bouyahya, A., & Oumhani, K. (2023). Meta-Analysis and Systematic Review of HLA DQ2/DQ8 in Adults with Celiac Disease. *International Journal of Molecular Sciences*, *24*(2).

Al-Toma, A., Volta, U., Auricchio, R., Castillejo, G., Sanders, D. S., Cellier, C., Mulder, C. J., & Lundin, K. E. A. (2019). European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. *United European Gastroenterol J*, *7*(5), 583-613.

Asvold, B. O., Langhammer, A., Rehn, T. A., Kjelvik, G., Grontvedt, T. V., Sorgjerd, E. P., Fenstad, J. S., Heggland, J., Holmen, O., Stuifbergen, M. C., Vikjord, S. A. A., Brumpton, B. M., Skjellegrind, H. K., Thingstad, P., Sund, E. R., Selbaek, G., Mork, P. J., Rangul, V., Hveem, K., . . . Krokstad, S. (2023). Cohort Profile Update: The HUNT Study, Norway. *Int J Epidemiol*, *52*(1), e80-e91.

Breedveld, A., & van Egmond, M. (2019). IgA and FcalphaRI: Pathological Roles and Therapeutic Opportunities. *Front Immunol*, *10*, 553.

Brown, I. S., Smith, J., & Rosty, C. (2012). Gastrointestinal pathology in celiac disease: a case series of 150 consecutive newly diagnosed patients. *Am J Clin Pathol*, *138*(1), 42-49.

Corazza, G. R., & Villanacci, V. (2005). Coeliac disease. *J Clin Pathol*, *58*(6), 573-574.

Di Sabatino, A., Vanoli, A., Giuffrida, P., Luinetti, O., Solcia, E., & Corazza, G. R. (2012). The function of tissue transglutaminase in celiac disease. *Autoimmun Rev*, *11*(10), 746-753.

Dickson, B. C., Streutker, C. J., & Chetty, R. (2006). Coeliac disease: an update for pathologists. *J Clin Pathol*, *59*(10), 1008-1016.

Eisen, G. M., Baron, T. H., Dominitz, J. A., Faigel, D. O., Goldstein, J. L., Johanson, J. F., Mallery, J. S., Raddawi, H. M., Vargo, J. J., Waring, J. P., Fanelli, R. D., & Wheeler-Harbough, J. (2002). Complications of upper GI endoscopy. *Gastrointest Endosc*, *55*(7), 784-793.

Green, P. H., Lebwohl, B., & Greywoode, R. (2015). Celiac disease. *J Allergy Clin Immunol*, *135*(5), 1099-1106; quiz 1107.

Green, P. H. R., & Guandalini, S. (2019). When Is Celiac Disease Celiac Disease? *Gastroenterology*, *157*(2), 293-294.

Gujral, N., Freeman, H. J., & Thomson, A. B. (2012). Celiac disease: prevalence, diagnosis, pathogenesis and treatment. *World J Gastroenterol*, *18*(42), 6036-6059.

Husby, S., Koletzko, S., Korponay-Szabo, I., Kurppa, K., Mearin, M. L., Ribes-Koninckx, C., Shamir, R., Troncone, R., Auricchio, R., Castillejo, G., Christensen, R., Dolinsek, J., Gillett, P., Hrobjartsson, A., Koltai, T., Maki, M., Nielsen, S. M., Popp, A., Stordal, K., . . . Wessels, M. (2020). European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease 2020. *J Pediatr Gastroenterol Nutr*, *70*(1), 141-156.

Iversen, R., & Sollid, L. M. (2023). The Immunobiology and Pathogenesis of Celiac Disease. *Annu Rev Pathol*, *18*, 47-70.

Krokstad, S., Langhammer, A., Hveem, K., Holmen, T. L., Midthjell, K., Stene, T. R., Bratberg, G., Heggland, J., & Holmen, J. (2013). Cohort Profile: the HUNT Study, Norway. *Int J Epidemiol*, *42*(4), 968-977.

Kvamme, J. M., Sørbye, S., Florholmen, J., & Halstensen, T. S. (2022). Population-based screening for celiac disease reveals that the majority of patients are undiagnosed and improve on a gluten-free diet. *Sci Rep*, *12*(1), 12647.

Lammers, K. M., Lu, R., Brownley, J., Lu, B., Gerard, C., Thomas, K., Rallabhandi, P., Shea-Donohue, T., Tamiz, A., Alkan, S., Netzel-Arnett, S., Antalis, T., Vogel, S. N., & Fasano, A. (2008). Gliadin induces an increase in intestinal permeability and zonulin release by binding to the chemokine receptor CXCR3. *Gastroenterology*, *135*(1), 194-204 e193.

Lebwohl, B., & Rubio-Tapia, A. (2021). Epidemiology, Presentation, and Diagnosis of Celiac Disease. *Gastroenterology*, *160*(1), 63-75.

Lebwohl, B., Sanders, D. S., & Green, P. H. R. (2018). Coeliac disease. *Lancet*, *391*(10115), 70-81.

Ludvigsson, J. F., Leffler, D. A., Bai, J. C., Biagi, F., Fasano, A., Green, P. H., Hadjivassiliou, M., Kaukinen, K., Kelly, C. P., Leonard, J. N., Lundin, K. E., Murray, J. A., Sanders, D. S., Walker, M. M., Zingone, F., & Ciacci, C. (2013). The Oslo definitions for coeliac disease and related terms. *Gut*, *62*(1), 43-52.

Maimaris, S., Schiepatti, A., Gabrielli, G. M., Costetti, M., Costa, S., Sanders, D. S., Zingone, F., Carroccio, A., Ciacci, C., Di Sabatino, A., & Biagi, F. (2020). Low prevalence of upper endoscopic gastrointestinal findings despite high frequency of alarm symptoms at the time of diagnosis in adult coeliac disease. *Eur J Gastroenterol Hepatol*, *32*(11), 1447-1451.

Matysiak-Budnik, T., Moura, I. C., Arcos-Fajardo, M., Lebreton, C., Menard, S., Candalh, C., Ben-Khalifa, K., Dugave, C., Tamouza, H., van Niel, G., Bouhnik, Y., Lamarque, D., Chaussade, S., Malamut, G., Cellier, C., Cerf-Bensussan, N., Monteiro, R. C., & Heyman, M. (2008). Secretory IgA mediates retrotranscytosis of intact gliadin peptides via the transferrin receptor in celiac disease. *J Exp Med*, *205*(1), 143-154.

Mearin, M. L., Ivarsson, A., & Dickey, W. (2005). Coeliac disease: is it time for mass screening? *Best Pract Res Clin Gastroenterol*, *19*(3), 441-452.

Merchea, A., Cullinane, D. C., Sawyer, M. D., Iqbal, C. W., Baron, T. H., Wigle, D., Sarr, M. G., & Zielinski, M. D. (2010). Esophagogastroduodenoscopy-associated gastrointestinal perforations: a single-center experience. *Surgery*, *148*(4), 876-880; discussion 881-872.

Mott, T., Gray, C., & Storey, J. (2022). A "no-biopsy" approach to diagnosing celiac disease. *J Fam Pract*, *71*(8), 359-361.

Rubin, J. E., & Crowe, S. E. (2020). Celiac Disease. *Ann Intern Med*, *172*(1), Itc1-itc16.

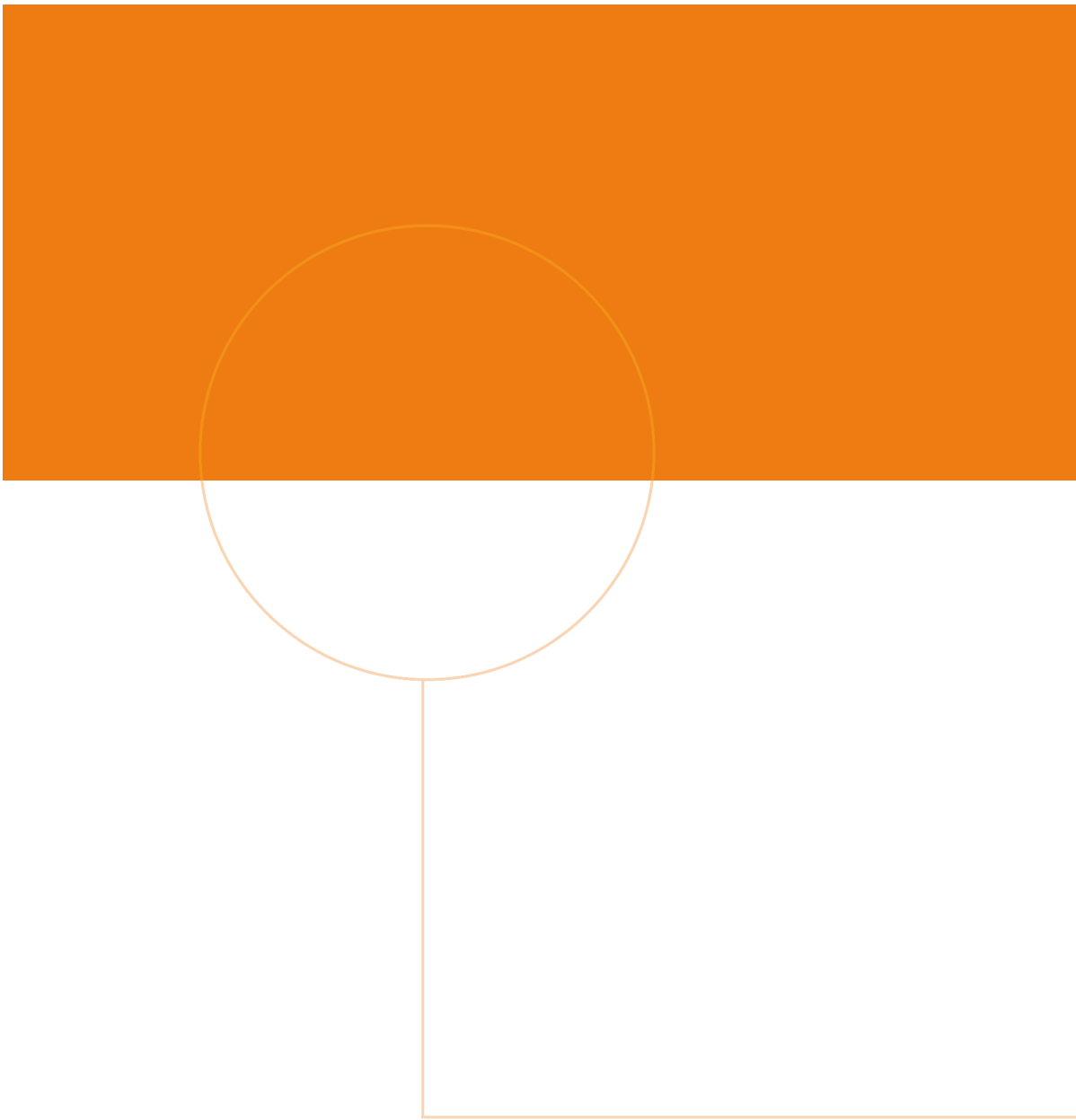
Schuppan, D., & Dieterich, W. (2020). *Epidemiology, pathogenesis, and clinical manifestations of celiac disease in adults*.

Singh, P., Singh, A. D., Ahuja, V., & Makharia, G. K. (2022). Who to screen and how to screen for celiac disease. *World J Gastroenterol*, *28*(32), 4493-4507.

Stefanolo, J. P., Zingone, F., Gizzi, C., Marsilio, I., Espinet, M. L., Smecuol, E. G., Khaouli, M., Moreno, M. L., Pinto-Sanchez, M. I., Niveloni, S. I., Verdu, E. F., Ciacci, C., & Bai, J. C. (2022). Upper gastrointestinal endoscopic findings in celiac disease at diagnosis: A multicenter international retrospective study. *World J Gastroenterol*, *28*(43), 6157-6167.

Vartdal, F. (2022, 13.04.2022). *HLA*. Retrieved 13.02.

Visse, R., & Nagase, H. (2003). Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. *Circ Res*, *92*(8), 827-839.



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