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ABSTRACT

Purpose Coeliac disease (CD) is a common disorder and affects about 1% of the population worldwide. CD in the Trøndelag Health Study (HUNT) is a population-based cohort study which was established to provide new knowledge about CD that can improve the diagnostics and management, prevent the onset or progression and expand the knowledge about the role of genetics of the disease.

Participants The cohort is based on the fourth wave of the population-based HUNT study (HUNT4), Norway, performed during 2017–2019, also including linkage to hospital records and the Norwegian Patient Registry (NPR). A total of 54 541 HUNT4 participants with available sera were screened for CD by serology. All seropositive participants were invited to a clinical assessment, including endoscopy with duodenal biopsies, during 2019–2023.

Findings to date A total of 1107 HUNT4 participants (2%) were seropositive for CD and 1048 were eligible for clinical assessment, including biopsy. Of these, 724 participants attended the clinical assessment and 482 were identified with CD. In addition, 371 participants with CD were identified through the hospital records and NPR. In total, 853 participants in HUNT4 with biopsy-verified CD diagnosis were identified.

Future plans All participants in the study will be invited to a follow-up assessment after at least 1 year, including repeated standard serological testing, endoscopy and tissue sampling. The collected data and material will be used to establish the true population-based prevalence of CD. The consequences of CD, including symptoms, deficiencies and comorbidity, will be investigated and possible triggers and predictors, will be studied. With access to serum samples from the previous HUNT surveys in HUNT Biobank, serological signs of CD in prediagnostic samples of seropositive individuals will be used. Genetic studies will identify new CD markers, assess genotype–phenotype links and explore gene–environment correlations.

Registration clinicaltrials.gov identifier: NCT04041622.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The population-based design with a high number of participants and high participation rate at baseline reduces selection bias.
⇒ The participants in the study are representative of the general population, and not selected for age, sex, health condition or social status.
⇒ The Norwegian birth number, unique to every Norwegian resident, provides an opportunity to link the HUNT data of every participant to his/her hospital records and national health registries to track his/her patient history, both in the past and in the future.
⇒ The ethnic homogenous population of Trøndelag leads to limited generalisability for people of non-European origin.
⇒ The study did not include participants below 20 years of age, so the paediatric and adolescent CD population is not included.

INTRODUCTION

Coeliac disease (CD) is an autoimmune condition triggered by the consumption of grains containing gluten in genetically predisposed individuals.[1] Gluten is the main storage protein in wheat, barley and rye.[2] Inflammation in the small intestine leads to villous atrophy and flattening of the intestinal mucosa.[3] The most common symptoms of CD include abdominal pain, increased bowel movements, weight loss, osteoporosis, anaemia and weakness.[4] The primary treatment for CD is a strict lifelong gluten-free diet.[5]

CD exists worldwide where gluten is a part of the diet and is among the most prevalent autoimmune disorders, affecting 0.5–2.4% of the general population globally.[6] Once considered as a condition in children of European origin, now CD is one of the most prevalent

lifelong disorders, affecting individuals of all ages across the globe.[7] Two systematic reviews conclude that the incidence of biopsy-confirmed CD is more common in women than men and approximately twice as common in children than in adults per 100 000 person years.[6 8] A notable upward trend in CD incidence has been observed from the latter half of the 20th century and continues into the 21st century across Western countries.[8] While CD was traditionally considered a paediatric disease, it is now diagnosed at any age.[7] However, most adults diagnosed with CD do not have past serological tests and therefore we do not know the actual disease onset. Former studies have also indicated a high ratio of undiagnosed to diagnosed CD cases.[9 10]

The pathogenesis of CD is a complex interaction between gluten, the immune response, and genetic and environmental factors.[11] The HLA-DQ2 and HLA-DQ8 genotypes are strongly associated with CD.[12 13] In addition, non-HLA genes have been identified, collectively explaining high heritability of the disease.[14 15] While individuals with a genetic susceptibility have an increased risk, the development of CD also requires environmental triggers. Data about the role of environmental factors in the risk of developing CD in adults are still limited.[16]

CD is associated with a higher occurrence of other autoimmune diseases.[17] Additionally, the risk of developing small intestinal lymphomas and adenocarcinomas is increased in individuals with CD.[18] However, due to these associations being established using hospital-based case series and a significant proportion of undiagnosed cases, the prevalence of comorbidity in the overall CD population is currently unknown.

The aim of our study was to provide new knowledge about CD that can improve the diagnostics and management, prevent the onset or progression and expand the knowledge about the role of genetics of the disease.

COHORT DESCRIPTION

Cohort basis

CD in the Trøndelag Health Study (HUNT) was established based on the fourth wave of the HUNT study (HUNT4) performed during 2017–2019.[19] The HUNT study is a population-based cohort study from former Nord-Trøndelag County, Norway (figure 1), established in the 1980s and is the largest collection of health data from the general population in Norway.[20–22] The population of Nord-Trøndelag is representative of Norway and other Western populations, except for the lack of large cities and immigrant populations. The population is stable, with low migration, making it well suited for longitudinal studies. In 2017, the population of the county was nearly 137 000 residents.[19] The study was designed to cover a broad range of health-related topics through repeated comprehensive questionnaires, clinical examinations, laboratory measurements and storage of biological samples. All individuals ≥20 years of age residing in the county were invited (online supplemental table S1). The HUNT data can be linked to national and local health registries by the unique identification number of all Norwegian residents ('the birth number').

The HUNT4 study

HUNT4 was performed between 29 August 2017 and 23 February 2019 with 56 042 participants out of 103 800 invitees (54.0% participation rate).[19] About 19 000 individuals have participated in all HUNT1–4 surveys with a total follow-up history since 1984–1986. Almost half of the participants in HUNT4 have participated in three HUNT surveys, and 60% of the participants have been followed from the previous HUNT3 survey (online supplemental figure S1). More women (54.6%) than men participated in HUNT4, which was similar to the previous HUNT surveys. The highest participation was in the age group of 50–59 years for women (19% participation rate) and 60–69 for men (21.3% participation rate). The lowest was in the age groups 20–29 years and >80 years. The HUNT4 survey's data collection included questionnaires and clinical measurements, in addition to collection of biological samples (blood, urine, faeces and saliva). A total of 849 different variables from HUNT4 are available in HUNT Databank. In addition, genetic material is available from almost all participants in HUNT2-4.[23]

HUNT Biobank

HUNT Biobank stores biological material from participants in HUNT2-4.[24 25] The biobank has a fully automated storage system with temperatures at −80°C (Azenta)[22] and a nitrogen storage unit which maintains a temperature of −187°C. The participants in HUNT4 provided blood samples at health examination stations in a non-fasting state. Fixed procedures for sampling, transport and storage were used. The blood samples were aliquoted and stored in the automated −80°C freezers at HUNT Biobank.

Data collection

The CD cohort was established based on the blood samples from the participants in HUNT4 (n=54 541) stored at HUNT Biobank (figure 2). Frozen serum from each participant was retrieved from HUNT Biobank and sent to Department of Medical Biochemistry, Oslo University Hospital for analyses with a new serological assay for simultaneous measurement of transglutaminase 2 (TG2) IgA and IgG antibodies.[26] A total of 1107 individuals (2%) were seropositive. Of these individuals, 59 were dead, had moved or withdrawn their consent, leaving 1048 individuals eligible for clinical assessment, including endoscopy with duodenal biopsy. All seropositive participants eligible for the study were invited through an invitational letter, including information about the endoscopic procedure, additional investigations and a written informed consent. A total of 59 seropositive participants already had a CD diagnosis, 32 before participation in HUNT4 and 27 after participation in HUNT4, but still took part in the clinical assessment, except endoscopy.

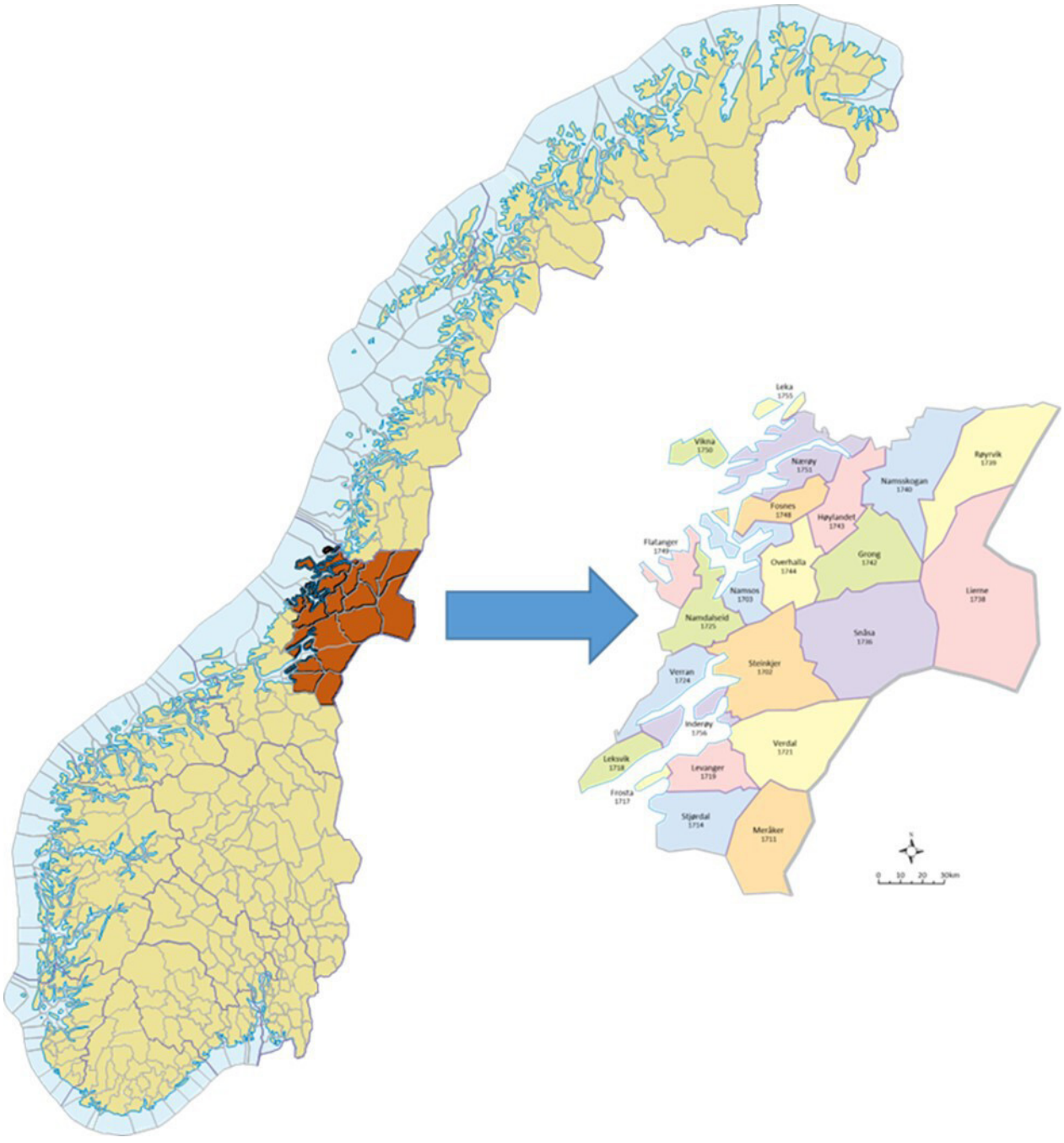

Figure 1 The former Nord-Trøndelag County, the Trøndelag Health Study's geographic area (the Norwegian Mapping Authority, Kartverket).

The clinical assessment included clinical chemistry (online supplemental table S2) with repeated serological testing using commercially available serological assays (TG2 IgA and deamidated gliadin peptide IgG antibodies, EliA Phadia 250, Thermo Fisher Scientific) and upper endoscopy with small intestinal biopsies. The endoscopies were

performed with standardised pictures taken from the duodenal pars horizontalis (D3) and the duodenal bulbus (D1) using Endobase (Olympus).[27] Six single-bite biopsies were collected in formalin, four from pars horizontalis (D3) and two from bulbus (D1), and four biopsies in RNAlater, two from pars horizontalis (D3) and two from bulbus (D1). Histopathological and immunohistochemical (CD3 staining) examinations were performed on the formalin-fixated biopsies at the Department of Pathology, St. Olav's Hospital, Trondheim University Hospital. As this was mass screening of the population and not case finding, strict criteria were used to diagnose CD. A diagnosis of CD required repeated positive serology at the time of endoscopy, Marsh grade 3[28 29] and exclusion of other possible causes of inflammation and atrophy, including infection with *Helicobacter pylori* by PCR testing of biopsies from the antrum and corpus of

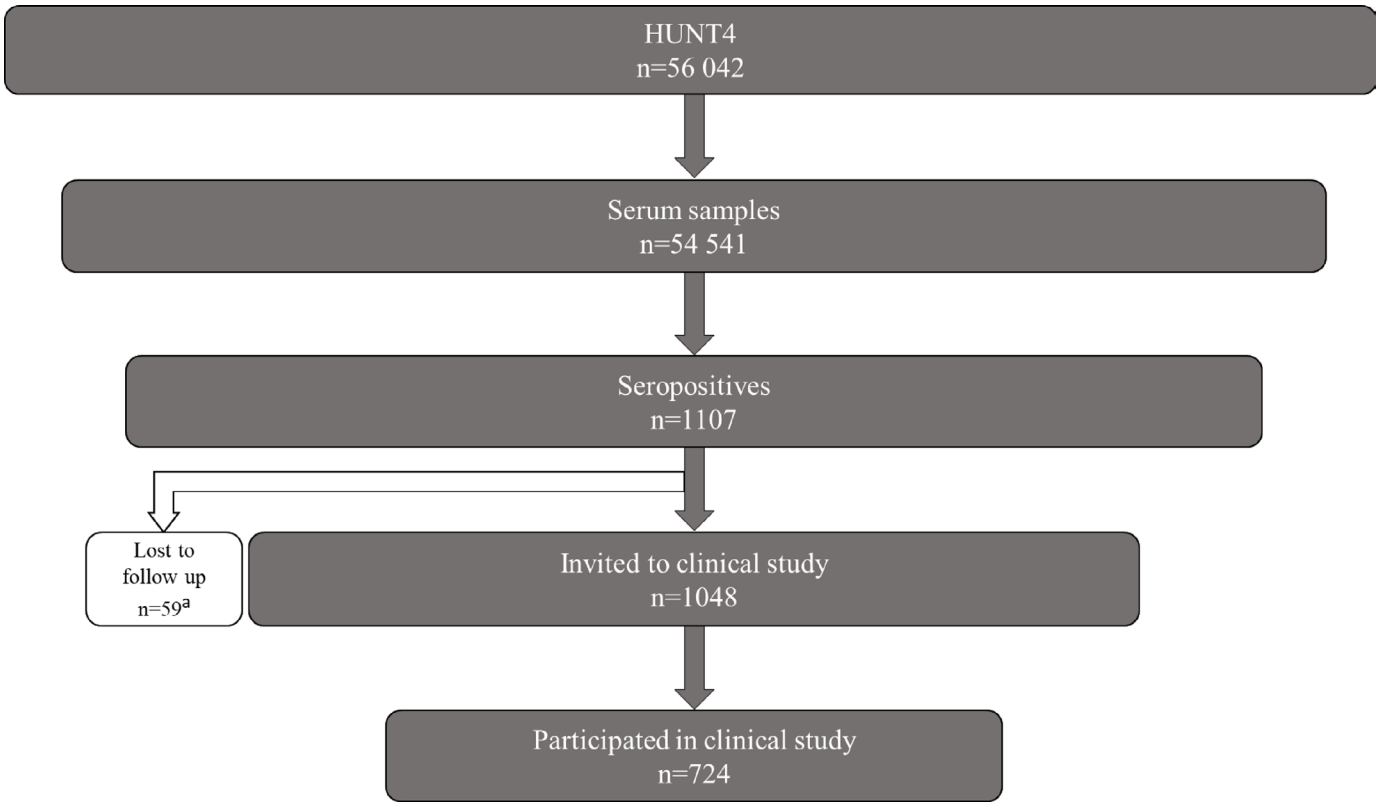

Figure 2 Number (n) of participants in each stage of the establishment of the coeliac disease cohort in the Trøndelag Health Study. [a]Dead, moved or refused consent.

the stomach and use of non-steroidal anti-inflammatory drugs or acetylsalicylic acid. Participants with Marsh grade below 3 were assessed as potential coeliacs and further recommended gluten-containing diet for a new diagnostic procedure after at least 1 year. The biopsies on RNAlater, in addition to serum, plasma, saliva and faeces were collected and stored at HUNT Biobank, which provided a source for future studies (online supplemental table S3a,b). The participants were also invited to bone mineral density measurements by dual-energy X-ray absorptiometry (DXA), performed at Levanger Hospital, Namsos Hospital or at Høvdinggården Medical Centre, Steinkjer, and to panoramic dental X-ray, orthopantomogram (OPG), performed at Levanger Dental Clinic. All participants in the clinical study were asked to fill in patient-reported outcome measures (PROMs; online supplemental table S4a–g). The PROMs included the Norwegian version of Short Form 36 Health Survey Questionnaire, Chalder Fatigue Scale, Hospital Anxiety and Depression Scale, Gastrointestinal Symptom Rating Scale-Irritable Bowel Syndrome, Coeliac Disease Symptom Index, Coeliac Disease Assessment Questionnaire and five in-house made questions about diet.[30–35]

All clinical research data were registered in WebCRF, a resource for online collection of research data, provided by the Norwegian University of Science and Technology (NTNU), and thereafter imported to HUNT Databank.[36] In addition, the clinical data were registered in DocuLive, the electronic hospital records at Levanger Hospital, and the endoscopic data were registered in Endobase (Olympus).[27 37] Results of the clinical chemical analyses, DXAs and OPGs were imported directly to HUNT Databank. The participants are invited to a 1-year follow-up with repeated serological testing, upper endoscopy with tissue sampling, collection of biological material and questionnaires.

Data linkage

To identify all participants in HUNT4 with CD, data were retrieved from the patient records at Nord-Trøndelag Hospital Trust (HNT; ie, Levanger Hospital and Namsos Hospital), St. Olav's Hospital and from NPR on all HUNT4 participants by linkage using the birth number (unique personal identification number).

At HNT and St. Olav's Hospital, the medical, surgical and radiological procedures performed are registered using the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures (NCSP) since 2006. The NCSP codes UJD02 (gastroscopy) and UJD05 (gastroscopy with biopsy) were used to identify HUNT participants with a possible CD diagnosis. Before 2006, rate codes were used to register the endoscopic procedures performed. Rate codes were part of the activity-based payment system for hospital care in Norway and were used to refund costs for medical procedures performed at the outpatient clinic.[38 39]

The NPR contains health information about all individuals who have received treatment or who are waiting for

Table 1 The number of participants in the fourth Trøndelag Health Study (n=56 042) with a CD diagnosis, by identifying data source

Data source	Number *	Seropositives, new CD†	Seropositives, known CD‡	Seronegatives or without serum, known CD‡	Total, with CD
CD in HUNT4	724	450	32	–	482
Nord-Trøndelag Hospital Trust/ St. Olav's Hospital	16 213	20	36	312	368
Norwegian Patient Registry	54 799	–	–	3§	3
Total		470	68	315	853¶

*The number of unique participants in each data source.
†Diagnosis date at or after participating date in HUNT4.
‡Diagnosis date before participating date in HUNT4.
§In total, 341 unique participants were identified with CD, but only three not already identified at Nord-Trøndelag Hospital Trust/St. Olav's Hospital.
¶The total number of unique participants with CD identified from all data sources.
CD, coeliac disease.

treatment in the specialist healthcare service in Norway.[40] The registry was searched for both primary and secondary diagnoses with the International Classification of Disease (ICD-10) diagnostic code for CD (K90.0).

Follow-up

All participants in the clinical study will be invited to a 1-year follow-up with repeated endoscopy and biopsy, in addition to repeated sampling of the biological material and repeated reporting on the questionnaires.

PATIENT AND PUBLIC INVOLVEMENT

The Norwegian Coeliac Society provided financial support for the project and has been involved in the planning of the study, but not the implementation or analyses.

Findings to date

Of the seropositive participants in HUNT4, 450 participants with a new, previously unknown CD diagnosis were identified after participation in HUNT4, in addition to 32 participants with known, previously diagnosed CD before participation in HUNT4 (table 1). Data on 16 213 HUNT4 participants were retrieved from the hospital records and a CD diagnosis was confirmed by histology in 312 individuals who were seronegative or without serum samples in HUNT4. In addition, 56 individuals that were seropositive in HUNT4 but did not attend the clinical assessment were identified with a histologically confirmed CD diagnosis through the hospital records. Of these 56, 20 individuals got their CD diagnoses after participation in HUNT4 and were defined as new CD cases, while the remaining 36 had already a known CD diagnosis before participation in HUNT4. The NPR accommodated data from 54 799 HUNT4 participants, collected from somatic hospitals and clinics (n=53 580) and from contract specialists in somatic disciplines (n=38 943). Of these, 341 individuals who were seronegative or without serum samples in HUNT4 were identified with a CD diagnosis, but only three participants with CD not already identified by the hospital record searches.

COLLABORATION

The CD project in HUNT4 was initiated in 2019 as a collaboration between researchers at NTNU, Levanger Hospital, St. Olav's Hospital, University of Oslo, Oslo University Hospital, Østfold University College, Karolinska Institute, Sweden, University of Groningen, the Netherlands and the Norwegian Coeliac Society.

Further details

Future plans

All seropositive participants, both those with confirmed and not confirmed CD, will be invited to a follow-up assessment after at least 1 year, including repeated standard serological testing, upper endoscopy and tissue sampling. Currently, the first clinical assessment is complete, and the follow-up assessment will be completed during 2024. The collected data will be used to establish the total population-based prevalence of CD. The serological data from the cohort will be analysed, including as part of a no-biopsy approach in diagnosing CD in adults, as in the paediatric population. The identification of all CD cases in an unselected population, including both the previously diagnosed and newly diagnosed cases, in addition to individuals with potential CD, is a unique resource for unbiased assessments of CD. The consequences of CD, including symptoms, deficiencies and comorbidity will be investigated, and possible triggers and predictors, both genetic and environmental, will be studied. Paediatric cohorts suggest that CD usually has its onset during childhood.[41] However, most adults diagnosed with CD do not have previous serological tests to assess if the disease might have occurred earlier in life. With access to serum samples from the previous HUNT2 and HUNT3 surveys in HUNT Biobank, serological signs of CD in prediagnostic samples of seropositive individuals will be used to

assess if CD might have occurred in adulthood or if there have been signs of the disease one to two decades ago in time.

Strengths and limitations

A major strength is the population-based design with a high number of participants and high participation rate at baseline, reducing selection bias. The participants in the study are representative of the general population, and not selected for age, sex, health condition or social status. However, the ethnic homogenous population of Trøndelag leads to limited generalisability for people of non-European origin.[19] The Norwegian birth number, unique to every Norwegian resident, provides an opportunity to link the HUNT data of every participant to his/her hospital records and national health registries to track his/her patient history, both in the past and in the future. Nearly 30 000 participants in HUNT4 have participated in more than one HUNT survey and have historical data and biological material stored in HUNT Databank and Biobank, respectively. This gives the possibility to study CD in a longitudinal and prospective manner. Participants in HUNT may also be recontacted for future studies, including collection of biological material.

The study was limited to the residents of Nord-Trøndelag County. The county is mainly representative of the Norwegian population, but the absence of a larger city causes low representation of a population in urban constituency. The study results may also be influenced by the lower level of participation by men in comparison with women, as well as the overall lower participation rate observed among both younger and older age groups.[19] The most represented age group was 40–79 years (78.6% of all women and 71.7% of all men participated). The study did not include participants below 20 years of age, so the paediatric and adolescent CD population is not included. The representation of participants >80 years of age in the clinical part of the study was low, reducing the validity of the results in the oldest population. Reasons for non-participation in this age group included long distance to the hospital, comorbidity and death before invitation to the clinical part of the study. Despite the possibility to link data from primary healthcare, it was not possible to identify participants with CD from this data source as the International Classification of Primary Care code for CD is D99, which includes several conditions and diseases unrelated to CD. However, in Norway, the CD diagnosis in adults is only confirmed in secondary healthcare after histological verification, minimising the effect of this limitation.

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Contributors Study design: ILA, LMS, KL, EN-J. Directing of the study's implementation: EN-J. Study conception: ILA, KH, TB, LPJ-J, LP, IJ, PeL, LMS, KL, EN-J. Data collection: PoL, ILA, PTE, PGM, ER, NB, RAK, DJW, RI, EN-J. Data analysis and interpretation: PoL, EN-J. Manuscript writing: PoL. Supervision: LMS, KL, EN-J. Critical revision of the article: PoL, ILA, PTE, ER, PGM, NB, RAK, DJW, RI, KH, TB, LPJ-J, LP, IJ, PeL, LMS, KL, EN-J. Final approval of the version to be published: PoL, ILA, PTE, ER, PGM, NB, RAK, DJW, RI, KH, TB, LPJ-J, LP, IJ, PeL, LMS, KL, EN-J. The guarantor: EN-J.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Regional Committee for Medical and Health Research Ethics, Central (reference number 7943). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The study data and material are available for research through application to HUNT Research Centre, as for other data and material from the main HUNT studies (https://hunt-db.medisin.ntnu.no/hunt-db/). All variables from the clinical assessment and PROMs are collected in HUNT Databank and the biological materials are stored in HUNT Biobank. A web application to HUNT Research Centre through the following link is needed to access data from the CD in HUNT: https://hunt-db.medisin.ntnu.no/hunt-db/ .In the web-application, the available variables and material from all the HUNT studies can be searched and ordered.

More information about data access and access to biological material is available at https://www.ntnu.edu/hunt/databank or by contacting kontakt@hunt.ntnu.no. Access to the clinical data is through application to the Research Department at Nord-Trøndelag Hospital Trust, contact email: forskningsavdelingen@hnt.no.

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Supplementary Table S1. Overview of the Trøndelag Health Study (HUNT) surveys.

Survey	Time period	Number of participants	Participation rate
HUNT1 (1)	1984-1986	77 212	89.4%
HUNT2 (2)	1995-1997	65 237	69.5%
HUNT3 (3)	2006-2008	50 807	54.1%
HUNT4 (4)	2017-2019	56 042	54.0%

1. Holmen J, Midthjell K, Forsén L, et al. [A health survey in Nord-Trøndelag 1984-86. Participation and comparison of attendants and non-attendants]. *Tidsskr Nor Laegeforen* 1990;110(15):1973-7.

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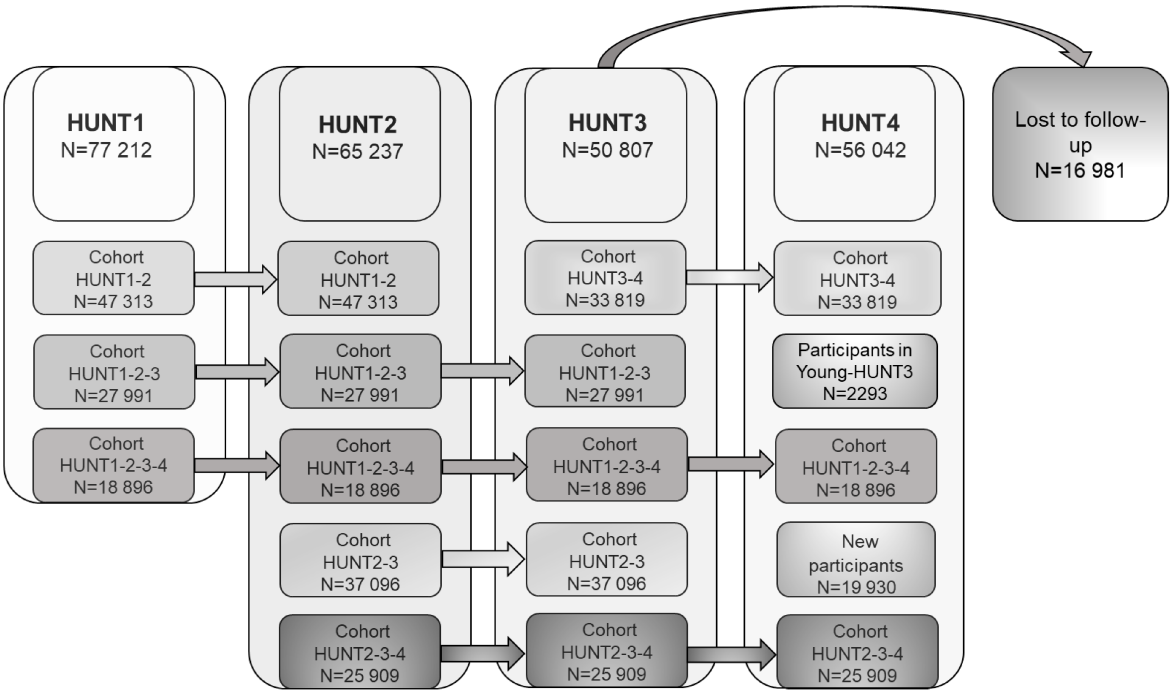

Supplementary Figure S1. Participation in the four Trøndelag Health Studies (HUNT1-4), by participation cohorts (Based on: Åsvold BO, Langhammer A, Rehn TA, et al. Cohort Profile Update: The HUNT Study, Norway. *Int J Epidemiol* 2023;52(1):e80-e91).

Supplementary Table S2. Clinical chemistry performed from blood samples collected in fasting state at Levanger Hospital at the day of endoscopy of participants in the clinical part of the Coeliac Disease in the Trøndelag Health Study (HUNT).

Analyses	**Units**	**Reference values**[a]
S-Vitamin D (25-OH-vitamin D)	nmol/L	75-150
S-Cobalamin (vitamin B12)	pmol/L	186-645
S-Folate	nmol/L	≥7
S-TSH (thyroid-stimulating hormone)	mIU/L	0.50-4.00
S-IgA anti-TG2 (transglutaminase 2)	kU/L	Negative: <7 Limit value: 7-10 Positive: >10
S-Anti-deamidated gliadin IgG	kU/L	Negative: <7 Limit value: 7-10 Positive: >10
S-Ionized calcium, pH 7.4	mmol/L	1.19-1.33
S-Zink	µmol/L	11.0-17.9
PS-ALT (alanine aminotransferase)	U/L	Women: 10-45 Men: 10-70
PS-Albumin	g/L	18–40 years old: 36-48 40–70 years old: 36-45 ≥70 years old: 34-45
PS-ALP (alkaline phosphatase)	U/L	35-105
PS-Calcium, total	mmol/L	Plasma: 3.5-4.4 Serum: 3.6-4.6

S-PTH (parathyroid hormone)	pmol/L	2.3-10.7
PS-Ferritin	µmol/L	Women: 20-167 Men: 30-383
PS-Glucose	mmol/L	Plasma: 4.2-6.3 Serum: 4.0-6.0
PS-GT (gamma-glutamyl transferase)	U/L	Women: 10-75 Men: 15-115
PS-IgA	g/L	1.1-3.7
PS-Creatinine	µmol/L	Women: 45-90 Men: 60-105
PS-Magnesium	mmol/L	0.71-0.94
PS-Bilirubin, total	µmol/L	5-25
B-Haemoglobin	g/dL	Women: 11.7-15.3 Men: 13.4-17.0
P-Selenium	µmol/L	0.6-1.8
B-HbA1c (glycated haemoglobin)	mmol/mol	28-40

a. Reference values, according to the performing laboratories. (1, 2)

Abbreviations: B, blood; Ig, immunoglobulin; P, plasma; S, serum

1. St.Olav`s Hospital Department of Clinical Chemistry.

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2. Fürst Medical Laboratory. https://www.furst.no/analyse-og-klinikk/ (accessed March 2023,).

Supplementary Table S3a. Biological material collected from participants in the clinical part of the Coeliac Disease in the Trøndelag Health Study (HUNT) and stored in HUNT Biobank.

Type of material	**Solution**	**Number of participants**
Serum	SST	757
Plasma	EDTA	757
Saliva	OG-500	750
Saliva	-	751
Tissue, duodenal pars horisontalis (D3) biopsies	RNAlater	687
Tissue, duodenal bulbus (D1) biopsies	RNAlater	636
Faeces	-	457

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Supplementary Table S3b. Storage type of the biological material collected from the participants in the clinical part of the Coeliac Disease in the Trøndelag Health Study (HUNT) and stored in HUNT Biobank.

Original tubes	**Aliquots**	**Number of aliquots**	**Storage type**
SST	Serum 0.5 ml Matrix[a]	6547	-80°C
SST	Serum 1.4 ml Matrix	1189	-80°C
SST	Serum 1.4 ml Matrix	751	Liquid Nitrogen
EDTA	Plasma 0.5 ml Matrix	5130	-80°C
EDTA	Plasma 1.4 ml Matrix	2435	-80°C
EDTA	Plasma 1.4 ml Matrix	754	Liquid Nitrogen
EDTA	Buffy-coat	755	-80°C
Faeces	DNA	14	-80°C
RNAlater horisontalis (D3)[b]	Tissue	687	Liquid Nitrogen
RNAlater bulbus (D1)[c]	Tissue	636	Liquid Nitrogen

[a]Thermo Scientific™ Matrix™ storage tubes

[b]Tissue samples from the duodenal pars horisontalis (D3) on RNAlater™ Stabilization Solution [c]Tissue samples from the duodenal bulbus (D1) on RNAlater™ Stabilization Solution

Abbreviations: DNA, deoxyribonucleic acid; EDTA, ethylenediamin tetra-acetic acid tubes; OG-500, Oragene™ DNA tubes, for the collection, stabilization, and transportation of DNA from saliva; RNA, ribonucleic acid; SST, serum separator tubes.

Supplementary Tables S4a-g. The patient reported outcome measures included in the Coeliac Disease in the Trøndelag Health Study**.**

Supplementary Table S4a. Short Form 36 (SF-36) Health Survey Questionnaire. (1)

Health	
In general, would you say your health is	Excellent Very good Good Fair Poor
Compared to one year ago	Much better now than one year ago Somewhat better now than one year ago About the same Somewhat worse now than one year ago Much worse now than one year ago
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?	Limited Yes, limited a little No, not at all

a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports b. Moderate activities, such as moving a table, pushing a vacuum cleaner, walking or gardening c. Lifting or carrying groceries d. Climbing several flights of stairs e. Climbing one flight of stairs f. Bending, kneeling, or stooping g. Walking more than a 2 km h. Walking some hundred meters i. Walking one hundred meters j. Bathing or dressing yourself	
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? a. Cut down the amount of time you spent on work or other activities	Yes No

b. Accomplished less than you would like c. Were limited in the kind of work or other activities d. Had difficulty performing the work or other activities (for example, it took extra effort)	
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? a. Cut down the amount of time you spent on work or other activities b. Accomplished less than you would like c. Didn't do work or other activities as carefully as usual	Yes No
During the past 4 weeks, to what extent has your physical health or emotional problems	Not at all Slightly Moderately

interfered with your normal social activities with family, friends, neighbours, or groups?	Quite a bit Extremely
How much bodily pain have you had during the past 4 weeks?	None Very mild Mild Moderate Severe Very severe
During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	Not at all A little bit Moderately Quite a bit Extremely
How much of the time during the past 4 weeks: a. Did you feel full of pep? b. Have you been a very nervous person? c. Have you felt so down in the dumps that nothing could cheer you up?	All of the time Most of the time A Good Bit of the Time Some of the Time A Little of the Time None of the Time

d. Have you felt calm and peaceful? e. Did you have a lot of energy? f. Have you felt downhearted and blue? g. Did you feel worn out? h. Have you been a happy person? i. Did you feel tired?	
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?	All of the time Most of the time Some of the time A little of the time None of the time
How TRUE or FALSE is each of the following statements for you. a. I seem to get sick a little easier than other people b. I am as healthy as anybody I know c. I expect my health to get worse d. My health is excellent	Definitely true Mostly true Don't know Mostly false Definitely false

1. Garratt AM, Stavem K. Measurement properties and normative data for the Norwegian SF-36: Results from a general population survey. *Health and Quality of Life Outcomes* 2017; 15:51.

Supplementary Table 4b. Chalder Fatigue Scale. (1)

Tiredness	
Do you have problems with tiredness?	Less than usual No more than usual More than usual Much more than usual
Do you need to rest more?	Less than usual No more than usual More than usual Much more than usual
Do you feel sleepy or drowsy?	Less than usual No more than usual More than usual Much more than usual
Do you have problems starting things?	Less than usual

	No more than usual More than usual Much more than usual
Do you lack energy?	Less than usual No more than usual More than usual Much more than usual
Do you have less strength in your muscles?	Less than usual No more than usual More than usual Much more than usual
Do you feel weak?	Less than usual No more than usual More than usual Much more than usual
Do you have difficulties concentrating?	Less than usual No more than usual More than usual Much more than usual

Do you make slips of the tongue when speaking?	Less than usual No more than usual More than usual Much more than usual
Do you find it more difficult to find the right word?	Less than usual No more than usual More than usual Much more than usual
How is your memory?	Better than usual No worse than usual Worse than usual Much worse than usual
If you are feeling tired now, how long has it been?	More than one week More than tree month Between tree and six months Six month and more
If you are feeling tired now, how much of the time do you feel it?	25% of the time 50% of the time 75% of the time

	All the time

1. Chalder T, Berelowitz G, Pawlikowska T, et al. Development of a fatigue scale. *Journal of Psychosomatic Research* 1993; 37: 147-53.

Supplementary Table 4c. Hospital Anxiety and Depression Scale (HADS). (1)

How do you feel?	
I feel nervous and restless	No Yes A lot of the time Most of the time
I still enjoy the things I used to enjoy	Definitely as much Not quite so much Only a little Hardly at all
I get a sort of frightened feeling as if something awful is about to happen	Very definitely and quite badly Yes, but not too badly A little, but it doesn't worry me Not at all
I can laugh and see the funny side	As much as I always could

of things	Not quite so much now Definitely not so much now Not at all
Worrying thoughts go through my mind	A great deal of the time A lot of the time From time to time Only occasionally
I feel cheerful	Not at all Not often Sometimes Most of the time
I can sit at ease and feel relaxed	Definitely Usually Not often Not at all
I feel as if I am slowed down	Nearly all the time Very often Sometimes Not at all

I get a sort of frightened feeling like 'butterflies' in the stomach	Not at all Occasionally Quite often Very often
I have lost interest in my appearance	Definitely I don't take as much care as I should I may not take quite as much care I take just as much care as ever
I feel restless as I have to be on the move	Very much indeed Quite a lot Not very much Not at all
I look forward with enjoyment to things	As much as I ever did Rather less than I used to Definitely less than I used to Hardly at all
I get sudden feeling of panic	Very often indeed Quite often Not very often

	Not at all
I can enjoy a good book or radio or TV program	Often Sometimes Not often Very seldom

1. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res* 2002; 52: 69-77.

Supplementary Table 4d. Gastrointestinal Symptom Rating Scale - Irritable Bowel Syndrome (GSRS-IBS). (1)

Stomach and bowels	
Have you been bothered by abdominal pain during the past week	No discomfort at all Minor discomfort Mild discomfort Moderate discomfort Moderately severe discomfort Severe discomfort Very severe discomfort

Have you been bothered by pain or discomfort in your abdomen relieved by a bowel action during the past week?	No discomfort at all Minor discomfort Mild discomfort Moderate discomfort Moderately severe discomfort Severe discomfort Very severe discomfort
Have you been bothered by a feeling of bloating during the past week?	No discomfort at all Minor discomfort Mild discomfort Moderate discomfort Moderately severe discomfort Severe discomfort Very severe discomfort
Have you been bothered by passing gas during the past week?	No discomfort at all Minor discomfort Mild discomfort Moderate discomfort Moderately severe discomfort

	Severe discomfort Very severe discomfort
Have you been bothered by constipation (problems emptying the bowel) during the past week?	No discomfort at all Minor discomfort Mild discomfort Moderate discomfort Moderately severe discomfort Severe discomfort Very severe discomfort
Have you been bothered by diarrhoea (frequent bowel movements) during the past week?	No discomfort at all Minor discomfort Mild discomfort Moderate discomfort Moderately severe discomfort Severe discomfort Very severe discomfort
Have you been bothered by loose bowel movements during the past week?	No discomfort at all Minor discomfort Mild discomfort

	Moderate discomfort Moderately severe discomfort Severe discomfort Very severe discomfort
Have you been bothered by hard stools during the past week?	No discomfort at all Minor discomfort Mild discomfort Moderate discomfort Moderately severe discomfort Severe discomfort Very severe discomfort
Have you been bothered by an urgent need to have a bowel movement (need to go to the toilet urgently to empty the bowel) during the past week?	No discomfort at all Minor discomfort Mild discomfort Moderate discomfort Moderately severe discomfort Severe discomfort Very severe discomfort

Have you been bothered by a feeling that your bowel was not completely emptied after having a bowel movement during the past week?	No discomfort at all Minor discomfort Mild discomfort Moderate discomfort Moderately severe discomfort Severe discomfort Very severe discomfort
Have you been bothered by feeling full shortly after you have started a meal during the past week?	No discomfort at all Minor discomfort Mild discomfort Moderate discomfort Moderately severe discomfort Severe discomfort Very severe discomfort
Have you been bothered by feeling full even long after you have stopped eating during the past week?	No discomfort at all Minor discomfort Mild discomfort Moderate discomfort Moderately severe discomfort

	Severe discomfort Very severe discomfort
Have you been bothered by visible swelling of your abdomen during the past week?	No discomfort at all Minor discomfort Mild discomfort Moderate discomfort Moderately severe discomfort Severe discomfort Very severe discomfort

1. Wiklund IK, Fullerton S, Hawkey CJ, et al. An irritable bowel syndrome-specific symptom questionnaire: development and validation. *Scand J Gastroenterol* 2003; 38(9): 947-54.

Supplementary Table 4e. Coeliac Disease Symptom Index. (1)

Symptoms	
Have you been bothered by pain or discomfort in the upper abdomen or the pit of the stomach during the past 4 weeks?	All of the time Most of the time Some of the time A little of the time None of the time

Have you been bothered by nausea during the past 4 weeks?	All of the time Most of the time Some of the time A little of the time None of the time
Have you been bothered by rumbling in your stomach during the past 4 weeks?	All of the time Most of the time Some of the time A little of the time None of the time
Has your stomach felt bloated during the past 4 weeks?	All of the time Most of the time Some of the time A little of the time None of the time
Have you been bothered by diarrhea during the past 4 weeks?	All of the time Most of the time Some of the time A little of the time

	None of the time
When going on the toilet, have you had the sensation of not completely emptying your bowels during the past 4 weeks?	All of the time Most of the time Some of the time A little of the time None of the time
Have you been bothered by hunger pains during the last 4 weeks?	All of the time Most of the time Some of the time A little of the time None of the time
Have you been bothered by low energy level during the past 4 weeks?	All of the time Most of the time Some of the time A little of the time None of the time
Have you been bothered by headaches during the past 4 weeks?	All of the time Most of the time Some of the time

	A little of the time None of the time
Have you had food cravings in the last 4 weeks?	All of the time Most of the time Some of the time A little of the time None of the time
Have you had loss of appetite during the past 4 weeks?	All of the time Most of the time Some of the time A little of the time None of the time
Related to Celiac Disease, how is your health?	Excellent Good Fair Poor Terrible
Overall, how is your health?	Excellent Good

	Fair Poor Terrible
How much physical pain have you had during the past 4 weeks?	None A little Some A good deal Very much
I am comfortable	Strongly agree Somewhat agree Neither agree nor disagree Somewhat disagree Strongly disagree
I am as healthy as anybody I know	Strongly agree Somewhat agree Neither agree nor disagree Somewhat disagree Strongly disagree

1. Leffler DA, Dennis M, Edwards George J, et al. A validated disease-specific symptom index for adults with celiac disease. *Clin Gastroenterol Hepatol.* 2009;7(12):1328-34, 34.e1-3.

Supplementary Table 4f. Coeliac Disease Assessment Questionnaire (CDAQ). (1)

Living with Coeliac Disease	
Have you worried that you might become ill after eating food prepared by others (for example, at other people's houses, restaurants, or cafés)?	Never Rarely Sometimes Often Always
Have you felt as though you might appear to be making a fuss about your dietary needs?	Never Rarely Sometimes Often Always
Have you felt that people misunderstood your coeliac disease or dietary needs (for example, thinking you follow a gluten-free	Never Rarely Sometimes

diet as a personal choice rather than for your coeliac disease)?	Often Always
Have you found it difficult to let people know they have misunderstood your coeliac disease or dietary needs?	Never Rarely Sometimes Often Always
Have you received unwanted attention because of your coeliac disease or dietary needs?	Never Rarely Sometimes Often Always
Have you felt guilty about the impact of your coeliac disease on friends and family?	Never Rarely Sometimes Often Always
Have you felt worried that a family member may have or could develop coeliac disease?	Never Rarely

	Sometimes Often Always
Have you felt concerned about developing a health problem related to your coeliac disease?	Never Rarely Sometimes Often Always
Have you been bothered by your bowel movements (for example loose stools, or constipation)?	Never Rarely Sometimes Often Always
Have you had bloating in your abdomen?	Never Rarely Sometimes Often Always

Have you had nausea or vomiting that you think was caused by your coeliac disease?	Never Rarely Sometimes Often Always
Have you had pain that you think was caused by your coeliac disease?	Never Rarely Sometimes Often Always
Have you had tiredness or a lack of energy that you think was caused by your coeliac disease?	Never Rarely Sometimes Often Always
Have your daily activities been limited by your coeliac disease?	Never Rarely Sometimes Often

	Always
Have you worried that you would become ill when you were not at home?	Never Rarely Sometimes Often Always
Have you felt isolated from others because of your coeliac disease?	Never Rarely Sometimes Often Always
Have you avoided social activities because of your coeliac disease?	Never Rarely Sometimes Often Always
Have you avoided going out to eat (for example, at a friend's house, restaurant, or café)?	Never Rarely Sometimes

	Often Always
Have you worried that you would accidentally eat or drink products that contain gluten?	Never Rarely Sometimes Often Always
Have you been concerned about cross-contamination (gluten-free food coming into contact with food that contains gluten)?	Never Rarely Sometimes Often Always
Have you felt uncomfortable refusing unsuitable food or drink from other people?	Never Rarely Sometimes Often Always
Have you felt down or in low spirits because of your coeliac disease?	Never Rarely

	Sometimes Often Always
have you felt you were a nuisance to other people because of your coeliac disease?	Never Rarely Sometimes Often Always
Have you felt guilty about other people buying gluten-free substitute foods for you?	Never Rarely Sometimes Often Always
Have you felt annoyed or frustrated about the cost of gluten-free substitute foods?	Never Rarely Sometimes Often Always

Have you had difficulty finding gluten-free food?	Never Rarely Sometimes Often Always
Have you craved food or drinks that contain gluten?	Never Rarely Sometimes Often Always
Have you been disappointed with the taste or texture of gluten-free substitutes?	Never Rarely Sometimes Often Always
Have you felt burdened by the time taken to find or make gluten-free food?	Never Rarely Sometimes Often

	Always
Have you had difficulty finding something to eat when you were not at home?	Never Rarely Sometimes Often Always
have you been frustrated by the choice of suitable food available (for example, in supermarkets, cafés or restaurants)?	Never Rarely Sometimes Often Always
Have you felt frustrated by having to plan ahead (for example, taking food with you, or choosing restaurants)?	Never Rarely Sometimes Often Always

1. Crocker H, Jenkinson C, Peters M. Quality of life in coeliac disease: item reduction, scale development and psychometric evaluation of the Coeliac Disease Assessment Questionnaire (CDAQ). *Aliment Pharmacol Ther* 2018; 48: 852-62.

Supplementary Table 4g. In-house made questions about diet.

Diet	
How much bread do you usually eat? -fine bread -coarse bread -wholemeal bread -fine crispbread -wholemeal crispbread -spelt bread -gluten-free bread -gluten-free crispbread	Never Rare ½-12+ slices per day
Breakfast groats: -oatmeal -whole graine muesli -breakfast mix -gluten-free oatmeal -gluten-free breakfast mix	How many times in a month OR in a week Never Rare 1-3 times in a month OR 1-8+ times in a week
Alcoholic beverages: -beer	How many times in a month OR in a week Never

-gluten-free bear Which brand, if gluten-free?	Rare 1-3 times in a month OR 1-7 times in a week
Various dishes and foods: -pizza -gluten-free pizza -pancakes -gluten free pancakes -sauces -gluten free sauces -gluten-containing spaghetti, pasta, noodles -gluten-free spaghetti, pasta, noodles -gluten-containing pastries, cakes, cookies, wafers, -gluten-free pastries, cakes, cookies, wafers	How many times in a month OR in a week Never Rare 1-3 times in a month OR 1-8+ times in a week
I have been following a gluten-free diet (in last 3 month)	None of the time A little of the time Some of the time

	Most of the time All the time