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Trends in the prevalence rates and predictive factors of coeliac disease: A long-term nationwide follow-up study

Juha Taavela[1,2] | Kalle Kurppa[1,3,4,5] | Tuija Jääskeläinen[6] | Niina E. Kaartinen[6] | Harri Rissanen[6] | Heini Huhtala[7] | Markku Mäki[1] | Katri Kaukinen[1,8]

[1]Celiac Disease Research Center, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland

[2]Department of Gastroenterology, Tampere University Hospital, Tampere, Finland

[3]Tampere Center for Child, Adolescent, and Maternal Health Research, Tampere University, Tampere, Finland

[4]Department of Pediatrics, Tampere University Hospital, Tampere, Finland

[5]University Consortium of Seinäjoki, Seinäjoki, Finland

[6]Finnish Institute for Health and Welfare, Helsinki, Finland

[7]Faculty of Social Sciences, Tampere University, Tampere, Finland

[8]Department of Internal Medicine, Tampere University Hospital, Tampere, Finland

Correspondence
Katri Kaukinen, Celiac Disease Research Center, Tampere University, Tampere, Finland.
Email: katri.kaukinen@tuni.fi

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Summary

Background: The prevalence of coeliac disease doubled in Finland from 1980 to 2000.

Aims: To investigate whether this increase is continuing and if there are specific patient-related factors predicting the development of coeliac disease at a population level.

Methods: We elicited comprehensive health data in the nationwide Health 2000 and Health 2011 surveys. Serum samples were taken for the measurement of tissue transglutaminase antibodies (TGA); subjects who were seropositive were tested for endomysial antibodies (EmA). Coeliac disease was defined either as a reported diagnosis or as positive TGA and EmA. The surveys comprised, respectively, 6379 and 4056 individuals, forming representative samples for 2,946,057 and 2,079,438 Finnish adults. Altogether 3254 individuals participating in both surveys comprised a prospective follow-up cohort.

Results: Prevalence of coeliac disease was 2.12% in 2000 and 2.40% in 2011 ($p = 0.156$). In the prospective cohort, 16 out of the 3254 (0.49%) subjects developed coeliac disease during follow-up from 2000 to 2011, with an annual incidence rate of 45 per 100,000 persons. Positive TGA without EmA (OR: 133, 95% CI: 30.3–584), TGA values in the upper normal range (51.1, 16.0–163), and after adjusting for TGA, previous autoimmune co-morbidity (8.39, 4.98–35.9) in 2000 increased the likelihood of subsequent coeliac disease.

Conclusions: The nationwide prevalence of coeliac disease kept on rising from 2.12% in 2000 to 2.40% in 2011 in Finland. Positive TGA without EmA, TGA titres in the upper normal range and a pre-existing autoimmune disease predisposed to coeliac disease during the 10-year follow-up.

1 | INTRODUCTION

The discovery of transglutaminase 2 (TGA) autoantibodies has revolutionised our understanding of coeliac disease epidemiology at the national level by enabling non-invasive screening at the population level.[1,2] Before the advent of serology, the prevalence of coeliac disease was only 0.01%–0.3%, while the current estimates are ~1%–2%, although there is substantial geographic variation.[1,3] Interestingly, the true prevalence, i.e., diagnosed and undiagnosed, of coeliac disease increased between the 1980s and before the 2000s.[4–6] The

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cause of this biological phenomenon and the likelihood of the trend continuing remain debatable.[7–12] According to data from registries of clinical diagnoses, a possible plateau has been suggested in coeliac disease.[11] However, the longitudinal evidence from unbiased population-representative cohorts that have undergone systematic screening for coeliac disease is limited.[3,13]

These screening studies have also revealed that the vast majority of coeliac disease patients go unrecognised and thus untreated and hence susceptible to various disease-associated complications.[14] In these circumstances, additional data on the predictive value of individual characteristics for coeliac disease could enable more efficient case-finding and improved screening strategies; particularly as untargeted mass screening is not currently considered justified.[15] It is also known that one-time seronegativity does not exclude coeliac disease for life, but the need for and yield of possible re-screening remains unclear.[16,17] A further relevant unresolved issue here is the long-term prognosis of the frequently seen borderline negative or low positive TGA levels without confirmed coeliac disease.[18]

In Finland, the true prevalence of coeliac disease doubled from 1.1% in the period 1978–80 to 2.0% in the period 2000–01.[4] We investigated whether this exceptionally high figure has further increased in the 2000s by utilising comparable population-representative cohorts. Furthermore, in a prospectively followed-up 10-year sub-cohort, we had an opportunity to explore the incidence of coeliac disease and factors associated with later coeliac disease in individuals without diagnosis in 2000.

2 | MATERIALS AND METHODS

2.1 | Patients and study design

The study was conducted in collaboration between Tampere University and the Finnish Institute for Health and Welfare (THL). It was based on the nationally representative Health 2000 and Health 2011 surveys carried out by THL.[19,20] The main aim of these surveys was to provide an up-to-date view of major public health problems in Finland. The surveys comprised a two-stage stratified cluster sampling and weighting scheme that estimates health statistics representative for same-aged Finnish population.[20–22]

In Health 2000, a total of 8028 adults ≥30 years of age living in mainland Finland were invited to participate in a health examination (including blood sampling), a health interview and to fill in questionnaires. To facilitate the two-stage stratified sampling, the sample frame was stratified regionally according to five university hospital regions (strata): namely those of Helsinki, Turku, Tampere, Kuopio and Oulu (Figure 1). In the first stage of sampling, 80 health centre districts were sampled as a cluster. The sample size for each health centre district was proportional to its proportion of the population. In the second stage, systematic random sampling was used to draw the sample from each health centre district using the nationwide population register. All living members of the original Health 2000 sample were reinvited to participate in Health 2011, and this group comprised the prospectively followed-up sub-cohort for the present study. The unweighted participation rate at any stage of the survey was 93% in Health 2000 and 73% in Health 2011.[19,20] Additional samples of younger adults were also invited for both studies, but they only completed a postal survey and were thus not included here.

The eligible Finnish adult population in Health 2000 amounted to 3,254,681 and in Health 2011 3,230,382 individuals, and the respective corresponding population-representative samples 8028 and 8177 individuals (Figure 1). The total population in Finland considering all ages was 5,181,115 in 2000 and 5,401,267 in 2011.[23] Only individuals on whom data were available on the status of diagnoses of possible previous coeliac disease and sera for the autoantibody analyses were included in the present analyses.

The participants were interviewed on either a separate home visit, at local health care facilities or by phone, and a health examination was conducted by a physician during the home visit or afterwards at the local health care facility. In addition, blood samples for research purposes were collected during the health examination and stored frozen at −70°C for later use. Data from patient data registries were obtained to supplement the medical information obtained through the survey.

The Health 2000 survey was approved by the Ethics Committee for Research in Epidemiology and Public Health in May 2000 and the Health 2011 survey by the Coordinating Ethics Committee in March 2011 at what was at that time the Hospital District of Helsinki and Uusimaa. Written informed consent was obtained from all participants in both years. All study data were analysed without direct information by which the participants could be identified.

2.2 | Clinical data

The following survey data were included in the present study: age, sex, level of education, employment status and current smoking status, likewise possible presence of gastrointestinal or autoimmune disease, coronary artery disease, type 2 diabetes and malignancy. The information on the presence of coeliac disease and other chronic conditions was self-reported or based on patient registry data. The cause of possible thyroid disease was not specified in the survey and was therefore not included under autoimmune diseases.

2.3 | Laboratory parameters and case definition

Plasma haemoglobin was analysed from the stored samples by THL, and anaemia was defined as haemoglobin <115 g/L in women and <132 g/L in men.[24] Serum IgA class TGA and endomysial antibodies (EmA) were analysed at the Tampere University Coeliac Disease Research Centre either by commercial Eu-tTG® (Eurospital S.p.A.; Health 2000) or by Celikey® (Phadia; Health 2011) test. Both serological assays use human recombinant transglutaminase as an antigen, and the results are given in arbitrary units (AU). Values ≥7.0 AU/mL for Eu-tTG and ≥5.0 AU/mL for Celikey were considered positive

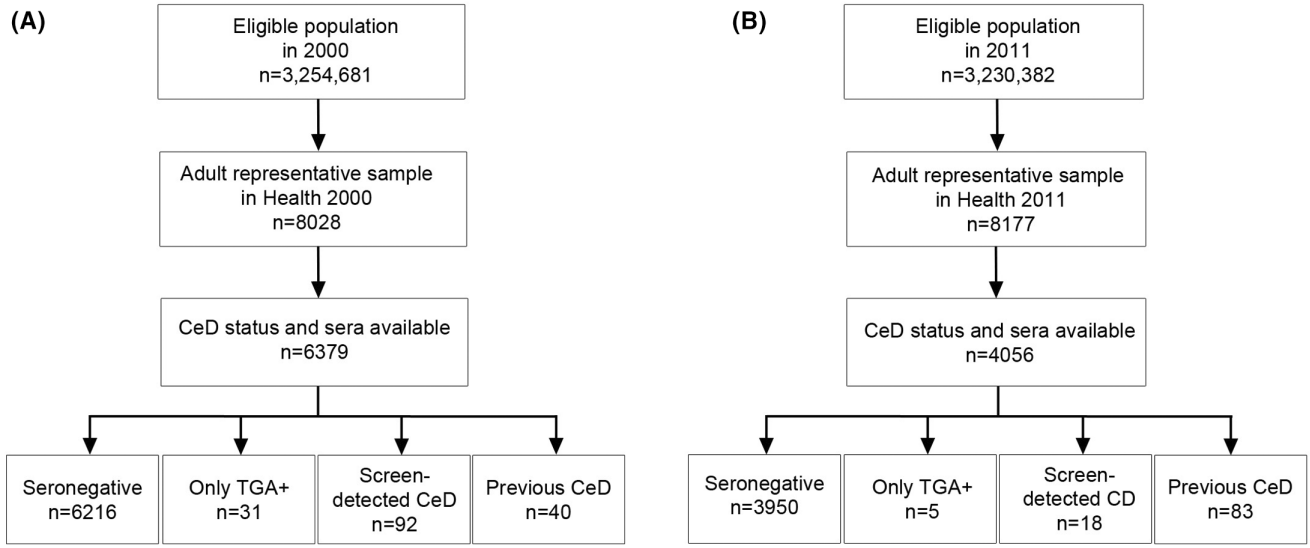

FIGURE 1 Flowchart of the separate Health 2000 (A) and Health 2011 survey (B) cohorts according to reported coeliac disease (CeD) and serum autoantibody status that represented population of Finland at respective time points. Individuals with available sera were assessed for tissue transglutaminase (TGA) and endomysial antibodies (EmA), and those with positivity for both autoantibodies were considered to have screen-detected CeD.

and further tested for EmA, which was determined using an indirect immunofluorescence method as described elsewhere.[25] A serum dilution of 1:≥5 for EmA was considered positive, and the sample was further diluted up to 1:4000. TGA titres in the normal range were divided into high normal titres, TGA between 5.1 and 6.9, and titres equal to and less than 5.0 were defined as low normal.

For the present study, subjects with either previously reported coeliac disease ("previous coeliac disease") or, regardless of the titre, positivity of both TGA and EmA ("screen-detected coeliac disease") were considered to fulfil the diagnostic criteria of coeliac disease.[26,27] The reported coeliac disease cases were scrutinised previously in the Mini-Finland Survey and Health 2000 as access to personal health data was available at that time. The analysis showed excellent concordance between the self-reported and biopsy-proven coeliac disease diagnoses.[4] The subjects with positive coeliac disease antibodies were notified and referred to healthcare to receive appropriate further diagnostics or follow-up in Mini-Finland Survey, Health 2000 and Health 2011 studies. Access to personal medical information was not available in the present study due to revised personal data protection regulations.

2.4 | Statistics

Descriptive data are given either as percentages or as means with ranges. Prevalence figures are given with 95% CIs. For the prevalence and incidence analyses, complex analyses function with provided weights was used in SPSS software (version 27; IBM). The inverse probability weights[22] were used to reduce bias due to non-participation and to provide nationally representative results. Post-stratification weights were calibrated according to age, gender, area and language in 2000. In 2011, the participation rate was lower and separate weights were created according to participation rate.[22] Statistical comparisons between the study groups were carried out with the chi-square test. In the complex sample analyses, the significance was tested using the adjusted *F* variant of the second-order Rao-Scott adjusted chi-square statistics. The likelihood for a later coeliac disease diagnosis in relation to different study variables in subjects without the diagnosis in 2000 was analysed with logistic regression to provide odds ratios (OR) with 95% CIs. A $p < 0.05$ was considered significant.

TABLE 1 Selected weight-adjusted characteristics in the Health 2000 and 2011 surveys in participants with coeliac disease status and sera for antibody measurements available.

	Health 2000, *n* = 6379	Health 2011, *n* = 4056
Age, mean (range), years	52 (30–99)	55 (29–97)
Females, %	52.6	53.3
University education, %	10.7	16.3
Unemployed, %	7.2	4.2
Coronary artery disease, %	7.6	5.9
Chronic gastrointestinal disease[a], %	12.3	11.7
Type 1 or 2 diabetes, %	5.6	7.9
Any malignancy, %	4.8	7.1
Current smoking, %	22.1	14.7

[a]Ulcerative colitis, Crohn's disease, lactose intolerance, irritable bowel syndrome.

3 | RESULTS

Data on patients fulfilling the inclusion criteria were available from 6379 and 4056 individuals in 2000 and 2011 respectively (Figure 1). Selected

TABLE 2 Prevalence of coeliac disease[a] in Finnish population according to age based on Health 2000 (total representative cohort $n = 2,946,057$) and Health 2011 ($n = 2,079,438$) cohorts.

Age group (years)	Health 2000, % (95% CI)			Health 2011, % (95% CI)			Difference in total 2000 vs. 2011
	Men	Women	Total	Men	Women	Total	
30–39	1.52 (0.78–2.94)	2.12 (1.29–3.47)	1.82 (1.21–2.72)	0.65 (0.46–2.59)	1.92 (0.88–4.12)	1.29 (0.65–2.55)	0.419
40–49	2.08 (1.30–3.30)	2.72 (1.84–3.99)	2.40 (1.79–3.20)	2.90 (1.68–4.98)	2.21 (1.09–4.45)	2.53 (1.58–4.02)	0.851
50–59	1.76 (0.95–3.24)	3.03 (2.03–4.49)	2.40 (1.75–3.30)	2.65 (1.56–4.45)	3.05 (1.92–4.81)	2.86 (2.01–4.06)	0.426
60–69	1.85 (0.94–3.61)	2.35 (1.34–4.08)	2.12 (1.36–3.28)	1.79 (0.85–3.73)	3.87 (2.49–5.98)	2.96 (2.02–4.30)	0.272
70-	1.24 (0.47–3.24)	2.00 (1.08–3.68)	1.72 (1.03–2.85)	1.17 (0.45–3.04)	2.63 (1.45–4.72)	2.01 (1.23–3.26)	0.804
All	1.74 (1.29–2.33)	2.47 (1.99–3.07)	2.12 (1.80–2.51)	1.95 (1.41–2.68)	2.80 (2.17–3.61)	2.40 (1.97–2.93)	0.156

[a]Previously diagnosed coeliac disease patients and screen-detected tissue transglutaminase and endomysial antibody-positive cases. There was no significant difference between men and women in any age categories in either 2000 or 2011.

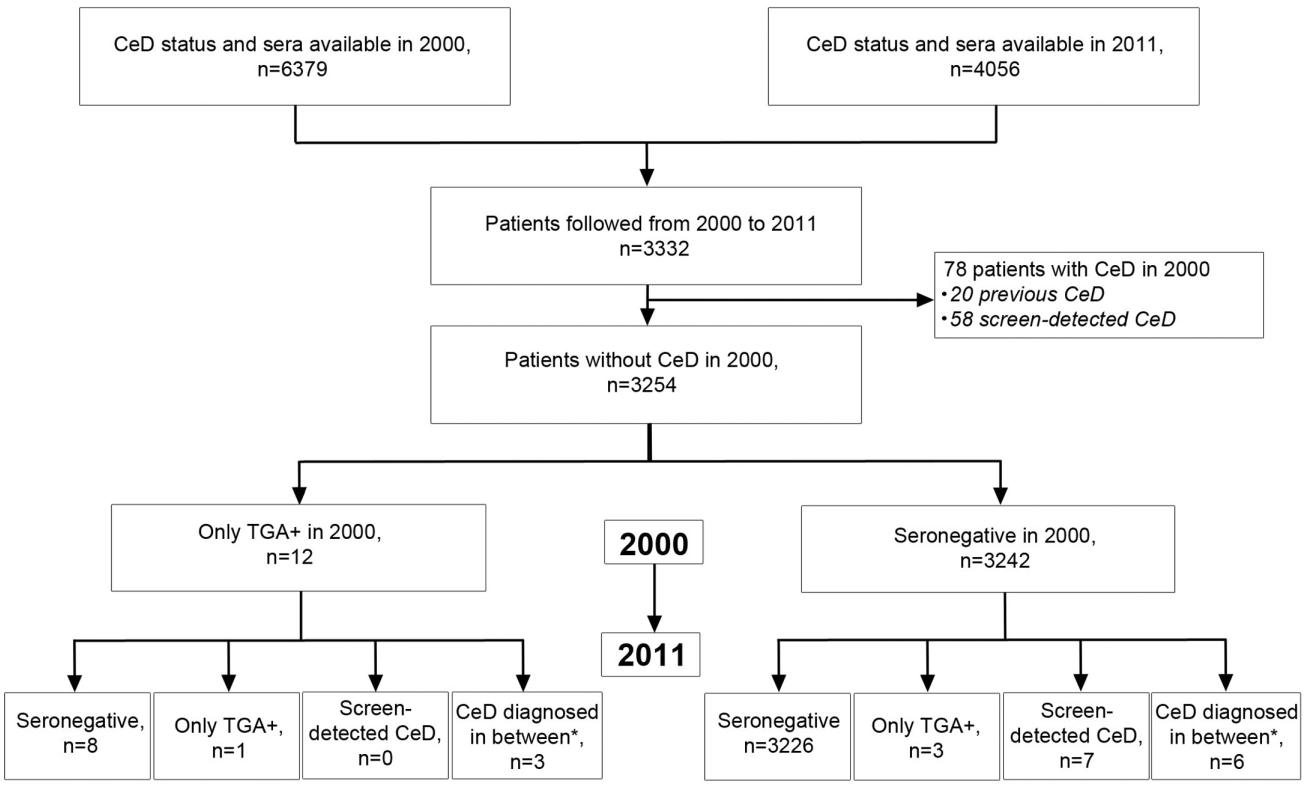

FIGURE 2 Flowchart of the follow-up cohort according to reported coeliac disease (CeD) and serum autoantibody status. The cohort consisted of individuals who participated in both Health 2000 and Health 2011 surveys on whom diagnostic data and sera were available. The sera were assessed for tissue transglutaminase (TGA) and endomysial antibodies (EmA), and subjects with positivity for both autoantibodies were considered to have screen-detected CeD. *Between 2000 and 2011.

characteristics of these participants are given in Table 1. There were altogether 132 coeliac disease patients in 2000, of whom 40 had a previous diagnosis and 92 were novel screen-detected (Figure 1A). The corresponding figures in 2011 were 83 previously diagnosed and 18 new screen-detected coeliac disease patients respectively (Figure 1B).

The weight-adjusted prevalence of coeliac disease was higher (2.40%) in 2011 than in 2000 (2.12%), but the difference was not statistically significant (Table 2). Similarly, the prevalence was numerically higher in all ages and in males and females in 2011, except in subjects aged 30–39 years. The highest prevalence was seen in women aged 60–69 years (3.87%) and the lowest in men aged 30–39 years (0.65%) in 2011. The total prevalence was higher in women in each age cohort except in those 40–49 years in 2011, but, again, the differences were not significant (Table 2).

Altogether 3332 individuals with available serum and coeliac disease status took part in both surveys and comprised the 10-year follow-up sub-cohort (Figure 2). Seventy-eight of these subjects had either previously diagnosed or screen-detected coeliac disease in 2000. Of the remaining 3254 subjects, 12 had positive TGA without EmA in 2000. Three (25%) of these 12 subjects (initial TGA range: 7.3–7.7 AU/mL) later received a diagnosis of coeliac disease between the years 2000 and 2011, while one (8%) remained seropositive

(TGA: 7.7 AU/mL in 2000, 5.2 AU/mL in 2011) but EmA negative and eight (67%; TGA: 7.1–10.0 AU/mL in 2000) converted to seronegative on a gluten-containing diet (Figure 2). In the seronegative patients, 13 (0.41%) subjects out of the 3242 had developed coeliac disease de novo in 2011, either due to clinical diagnosis between 2000 and 2011 ($n=7$, 0.22%) or because of new TGA and EmA positivity ($n=6$, 0.19%). Four (0.12%) previously seronegative patients had positive TGA but negative EmA in 2011 (Figure 2). A more detailed flow-chart divided based on TGA titers is provided as a Figure S1.

In total, 16 subjects thus developed coeliac disease between 2000 and 2011 (Figure 2), giving an annual incidence of 45 (95% CI: 27–75) per 100,000 persons for the whole cohort, and separately 44 (22–88) per 100,000 for men and 45 (24–86) per 100,000 for women. Factors increasing the likelihood for later coeliac disease diagnosis in crude analysis were presence of a co-existing autoimmune disease – including type 1 diabetes, although there was only one subject–, anaemia and positive or high normal TGA values with negative EmA in 2000, whereas sex had no significant effect (Table 3). The significance of anaemia disappeared after adjusting for TGA titres 2000 (Table 3).

4 | DISCUSSION

We found the prevalence of coeliac disease in Finland to be 2.1% in 2000 and 2.4% in 2011, these being among the highest reported nationwide percentages. In our earlier study, the corresponding figure in 1978–1980 was 1.1%.[3,4] It thus appears that the prevalence has continued to rise despite already being exceptionally high, although the steepest increase may have levelled off (Figure 3). Of note, although there were no statistically significant sex differences, in line with previous evidence[3] women had higher prevalence in almost all age groups, including ~3.9% among those aged 60–69 years.

No comparable studies involving screening of nationwide representative cohorts in three time points are available, but some studies have reported prevalence trends over time. Rubio-Tapia et al[5] reported an increase of coeliac disease seropositivity from 0.2% in 1948–54 to 0.8–0.9% in 1995–2003 in a male cohort, and the same group reported a prevalence of 1.1% in Olmsted County, USA, in 2006–11.[27,28] Catassi et al[29] observed a change from 0.2% in 1974 to 0.4% in 1989 in Washington County, while figures between 0.6 and 0.8% in 2009–2014 and 0.7% in 2009–2010 were observed in the NHANES cohort.[30,31] Horwitz et al[32] found markedly higher prevalence of coeliac disease (2.6%) than reported previously from Denmark, but the screening was limited to adolescents living on Funen Island. Finally, in a recent meta-analysis, the prevalence of coeliac disease increased from 0.6% in 1991–2000 to 0.8% in 2001–16,[3] although there was major heterogeneity between studies.

In general, the prevalence thus seems to be increasing over time, although comparison of the studies is hampered by limited geographical coverage, diverse demographic and ethnic composition,

TABLE 3 Likelihood of later coeliac disease (CeD, $n=16$) in relation to study variables in subjects without coeliac disease in 2000 ($n=3254$), both in crude analysis and after adjusting for tissue transglutaminase antibody titres (TGA) in 2000.

			Crude			Adjusted		
	Subjects	CeD	OR	95% CI	*p* value	OR	95% CI	*p* value
Sex								
Male	1459	7	1			1.00		
Female	1795	9	1.05	0.38–2.81	0.930	0.64	0.22–1.83	0.403
Anaemia								
No	3114	14	1			1.00		
Yes	100	2	4.52	1.32–16.6	0.030	4.13	0.85–20.2	0.080
Other AID[a]								
No	2963	10	1			1.00		
Yes	285	6	8.39	3.98–35.9	<0.001	8.96	3.03–26.5	<0.001
Type 1 diabetes								
No	3241	12	1			1.00		
Yes	13	1	17.9	2.19–147	<0.001	12.1	1.39–105	0.024
TGA in 2000								
Low normal 0–5.0	3199	8	1					
High normal 5.1–6.9	43	5	52.5	16.4–168	<0.001			
Positive ≥7.0[b]	12	3	133	30.3–584	<0.001			

Abbreviation: AID, autoimmune disease; OR, odds ratio.

[a]Type 1 diabetes, psoriasis, rheumatoid arthritis, spondylarthritis, ulcerative colitis, Crohn's disease, systemic lupus erythematosus, Sjögren's disease, sarcoidosis, lichen sclerosus.

[b]Negative endomysial antibodies, commercial TGA kit Eu-tTG®.

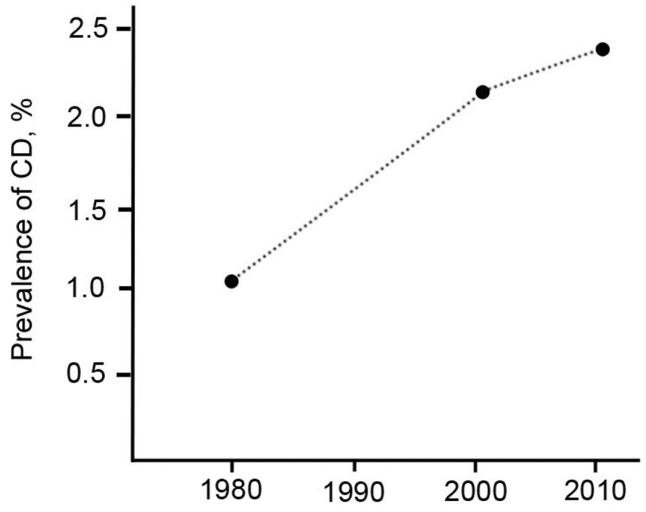

FIGURE 3 Prevalence of coeliac disease (CeD) over 30 years in Finland based on national representative cohorts in the present study (2000, 2011) and an earlier study by Lohi et al.[4]

and the use of different testing strategies and criteria for coeliac disease.[3] Neither the temporal changes nor population differences can be explicitly explained by alterations in genetics[33] or the consumption of gluten-containing cereals,[34] indicating a role of environmental factors. Further support for this is afforded, for example, by the variations observed in prevalence between geographically adjacent nations and even within countries,[7,35,36] rapid changes of the local incidence[36] and latitude and season of birth effects.[35] The present results are also line with previous findings that the prevalence of coeliac disease increases with age,[6] indicating that the disease process could start also at later age depending on the individual genetic risk, diet and other environmental exposures.[37,38] This increases the cumulative prevalence since the patients nowadays do not seem to have markedly increased mortality.[39] At present, however, the ultimate reasons behind these secular and age-related increases of coeliac disease prevalence remain to be elucidated.

The annual incidence rate (IR) of new coeliac disease diagnoses – 45/100,000 persons – among the once screened sub-cohort was relatively high. There is limited research on this issue, but in our earlier study on an elderly population cohort of people over 55 years of age the corresponding EmA-positive figure was 60/100,000, while Choung et al. reported an IR of 16/100,000 among one-time seronegative adults.[6,17] Direct comparison between the studies is again challenging due to different designs and definitions of coeliac disease. Duration of follow-up is also important, as isolated TGA positivity may turn to coeliac disease only after an extended period of time. The corresponding IR for a later diagnosis has been markedly higher, up to 221/100,000, among once-seronegative relatives.[16] Unfortunately, we had no data on the familial predisposition to coeliac disease.

Presence of autoimmune disease and anaemia in 2000 predicted later coeliac disease in a crude analysis, but the latter disappeared after adjusting for concurrent TGA positivity. While the association of coeliac disease with other autoimmunity is well established,[40–42] there is a scarcity of long-term follow-up data on the actual risk. Choung et al[17] reported a previous autoimmune disease to increase the likelihood of coeliac disease with a factor of 2.5 during 10-year follow-up. The OR was even higher in our systemically tested individuals, thereby supporting active surveillance of this at-risk population.[17,43] Of note, although the significance of anaemia vanished after the adjustment, previous data show that low haemoglobin could be associated with hastened disease process in coeliac disease, which underlines the need for more studies on this issue.[44]

TGA seropositivity and also TGA value in the upper normal range also predicted later coeliac disease in EmA negative individuals. The latter observation is remarkable, as this ambiguous finding is likely increasing due to more extensive screening.[43,45,46] Further complicating the situation, most cases with low positive TGA converted to seronegative while reporting consuming gluten. This phenomenon has mainly been reported in children while adult data remain scarce.[17,47,48] The frequency of these cases may in part reflect the intrinsic properties and chosen cut-off of a given seroassay,[49] and whether they do indeed have truly transient autoimmunity or merely a temporary fluctuation remains unclear.[17,50] Of note, participants in 2000 were informed about their TGA values, which may have affected to their gluten intake. More research is called for, but for now at least active surveillance of subjects with borderline TGA values is recommended.

The main strengths of the present study are the systematic screening of large and nationally representative cohorts, the availability of various individual-level data and the use of well-defined seroassays for coeliac disease. As a limitation, the participation rate was lower in 2011 than in 2000, although this was statistically adjusted for.[22] Furthermore, we were not able to collect the detailed clinical presentation or original histological reports of individual participants. However, there was an excellent concordance between the self-reported and confirmed coeliac disease diagnoses in our previous study.[4] Moreover, the double-positive serology used provides high specificity and has also been used in earlier epidemiological studies on coeliac disease.[2,27,51,52] In fact, this approach may offer less biased outcome than the burdensome and frequently declined endoscopy. It must, however, be emphasised that a part of particularly elderly patients may present with false-negative coeliac disease serology and thus might thus have been missed.[6,53] An additional limitation was the lack of genetic data and information on familial risk for coeliac disease.[16]

To conclude, we found an increasing prevalence of coeliac disease in a nationally representative adult cohort with already high figures, although the rise might be less steep than before. Individuals with some other autoimmune disease or TGA positivity with negative EmA and, of particular interest, also those with borderline negative TGA values were at significantly increased risk of later coeliac disease during follow-up.

AUTHOR CONTRIBUTIONS

Juha Taavela: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; writing – original draft; writing – review and editing. **Kalle Kurppa:** Conceptualization; formal

analysis; funding acquisition; investigation; writing – original draft; writing – review and editing. **Tuija Jääskeläinen:** Formal analysis; investigation; writing – review and editing. **Niina Kaartinen:** Investigation; writing – review and editing. **Harri Rissanen:** Formal analysis; investigation; writing – review and editing. **Heini Huhtala:** Methodology; writing – review and editing. **Markku Maki:** Supervision; writing – review and editing. **Katri Kaukinen:** Conceptualization; formal analysis; funding acquisition; investigation; supervision; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

None declared.

AUTHORSHIP

Guarantor of the article: Katri Kaukinen, Celiac Disease Research Center, Tampere University, Tampere, Finland; katri.kaukinen@tuni.fi.

ORCID

Juha Taavela https://orcid.org/0000-0003-3948-9555
Kalle Kurppa https://orcid.org/0000-0003-4757-2164
Katri Kaukinen https://orcid.org/0000-0002-5046-8133

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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