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Increasing prevalence of coeliac disease over time

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SUMMARY

Background
The number of coeliac disease diagnoses has increased in the recent past and according to screening studies, the total prevalence of the disorder is around 1%.

Aim
To establish whether the increased number of coeliac disease cases reflects a true rise in disease frequency.

Methods
The total prevalence of coeliac disease was determined in two population-based samples representing the Finnish adult population in 1978–80 and 2000–01 and comprising 8000 and 8028 individuals, respectively. Both clinically–diagnosed coeliac disease patients and previously unrecognized cases identified by serum endomysial antibodies were taken into account.

Results
Only two (clinical prevalence of 0.03%) patients had been diagnosed on clinical grounds in 1978–80, in contrast to 32 (0.52%) in 2000–01. The prevalence of earlier unrecognized cases increased statistically significantly from 1.03% to 1.47% during the same period. This yields a total prevalence of coeliac disease of 1.05% in 1978–80 and 1.99% in 2000–01.

Conclusions
The total prevalence of coeliac disease seems to have doubled in Finland during the last two decades, and the increase cannot be attributed to the better detection rate. The environmental factors responsible for the increasing prevalence of the disorder are issues for further studies.

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INTRODUCTION

Coeliac disease, which is induced by ingestion of cereal gluten, is a chronic autoimmune-mediated disease with both intestinal and extraintestinal manifestations. Until the late 1970s, the suspicion of coeliac disease was based mainly on clinical symptoms such as diarrhoea, malabsorption and weight loss. The disease was considered to be rare; the prevalence was estimated to be as low as 0.03% worldwide.[1] Subsequently, the disease has been found more frequently in adults suffering from a variety of atypical symptoms and even in asymptomatic subjects.[1] With realization of the diversity of its manifestations and the advent of highly sensitive and specific serological tests, endomysial and tissue transglutaminase antibody assays,[2] the increasing trend in incidence figures could be verified.[3–5] Furthermore, the tests enabled mass-screening of populations, and the prevalence of the disease was soon found to be around 1% in both Europe and the United States.[6–9]

The changed prevalence figures have sparked off debate as to whether the increasing prevalence of the condition reflects a true rise in prevalence in the course of time or whether it is due simply to the better detection rate.[4] It is intriguing to speculate that such an increase could be a phenomenon parallel to that observed in type 1 diabetes, other autoimmune disorders and allergic diseases.[10] To assess the prevalence of the disease over time, we defined it in two representative national population-based cohorts collected in 1978–80 and in 2000–01. Firstly, we determined the clinical prevalence of the disease in both cohorts and secondly, we screened the rest of the participants using highly sensitive and specific screening tools to identify unrecognized cases. By adding together the numbers of clinically diagnosed coeliac disease patients and the screen-detected previously unrecognized cases we arrived at the total prevalence of the disorder in the two cohorts collected two decades apart. Our hypothesis was that a true rise in disease prevalence is in fact under way.

MATERIALS AND METHODS

Study populations

The prevalence of coeliac disease was determined in two cross-sectional population cohorts representing the adult populations in Finland at two different time-points. The first sampling, the Mini-Finland Health Survey, was carried out in 1978–1980. Details of the study design and the baseline results are extensively reported elsewhere.[11, 12] In brief, a nationally representative sample of 8000 persons has been drawn from the population aged 30 and over by a stratified two-stage cluster sampling design planned by Statistics Finland. The study population was drawn from 40 areas in different parts of the country. The participants attended a health examination, which included interviews, questionnaires, drawing of blood samples and a clinical examination by a physician. The participation rate was 90% (n = 7217).

The second nationally representative population sampling designed by professional epidemiologists was carried out in 2000–2001. The basic data from this Health 2000 Survey have recently been published by The National Public Health Institute, and one of the goals of the survey was to determine changes in population health since 1978–80 by comparing health issues with the Mini-Finland Health Survey.[13] In summary, the two-stage cluster sample of 8028 persons aged 30 or more was drawn from 80 health service districts throughout the country. The survey comprised interviews, questionnaires, measurements and clinical examinations principally similar to those in the Mini-Finland Survey of 1978–80. The participation rate was 84% (n = 6770).

A flow-chart of the present study is presented in Figure 1 and a comparison of the cohorts by several variables in Table 1. The non-participants did not markedly differ from the participants in socio-demographic characteristics in both surveys.[11, 13] According to our follow-up data no differences were detected between the participants and non-participants as regards mortality and morbidity. There is no reason to believe that non-participants differed from participants by indicators connected to coeliac disease.

All participants gave informed consent in both health surveys. The Ethical Committee of Tampere University Hospital approved the study protocol.

Assessment of coeliac disease

Previously diagnosed coeliac disease patients

All participants in the Mini-Finland Survey in 1978–80 were interviewed and asked whether they had any chronic diseases. Chronic disorders were also recorded in the course of the clinical examinations.

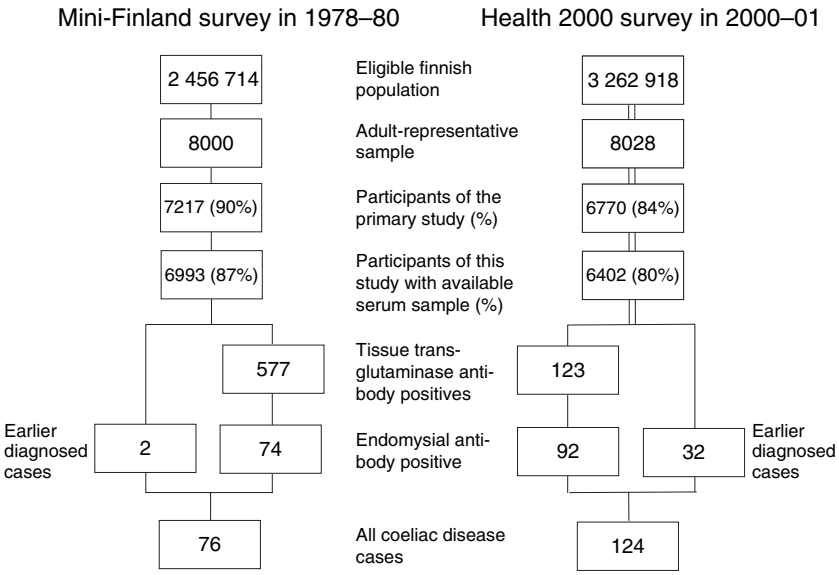

Figure 1. Flow-chart of the present study.

Table 1. The age- and sex-adjusted characteristics of the study participants in the Mini-Finland- and Health 2000 surveys

	Mini-Finland survey	Health 2000 survey	*P*-value
Males, %*	45.8	47.6	0.02
Mean age, years†	51.0	52.8	<0.001
Higher education, %	11.5	28.7	<0.001
Mean serum cholesterol, mmol/L	6.9	5.9	<0.001
Current smoker, %	23.5	25.1	0.05
Mean BMI, kg/m^2	25.8	26.9	<0.001
Any chronic illness‡,%	45.9	51.5	<0.001
Coronary disease‡, %	10.2	7.6	<0.001
Diabetes‡, %	4.7	5.6	0.04
Cancer, any‡, %	2.4	4.7	<0.001

* Adjusted for age; † Adjusted for sex; ‡ Self-reported.

In the Health 2000 Survey, participants were asked by structured questionnaire whether a physician had previously diagnosed coeliac disease or dermatitis herpetiformis. The physician responsible for the clinical examination recorded all chronic diseases in the participants.

In 2004, we further scrutinized the reported diagnoses of coeliac disease and dermatitis herpetiformis of both cohorts by case record data.

As dermatitis herpetiformis with skin manifestations is one form of coeliac disease,[1, 14] cases fulfilling the diagnostic criteria for coeliac disease or dermatitis herpetiformis were included. The criteria for coeliac disease were villous atrophy with crypt hyperplasia in a small-bowel biopsy specimen and clinical or histological recovery on a gluten-free diet.[15] From the 1970s the diagnosis of dermatitis herpetiformis has been based on the demonstration of pathognomic granular IgA deposits in the dermal papillae by direct immunofluorescence examination, and prior to the development of this method on a typical clinical picture.[1, 14]

Only the scrutinized cases fulfilling the above-mentioned diagnostic criteria for coeliac disease or dermatitis herpetiformis were used in numerators in the calculations of clinical prevalences.

Screening of unrecognized coeliac disease cases

The previously collected blood samples were stored at −20 °C for later analysis. In the Mini-Finland survey, a total of 6993 (3771 females) serum samples were available for determination of coeliac disease antibodies. This compares with 6402 (3527 females) samples in the Health 2000 survey. These figures were used as denominators in calculating the prevalence of coeliac disease. The availability of sera reduced the excellent participation rates by 3–4% in both cohorts; selection of these subjects did not depend on issues related to coeliac disease and is not likely to influence the results. The age and sex distributions of the participants with available serum samples are given in Table 2.

Table 2. The age and sex distributions of the participants with available serum sample in the Mini-Finland and Health 2000 surveys

	n (Female %)	
Age	Mini-Finland year 1978–80	Health 2000 year 2000–01
30–44	2681 (50)	2132 (53)
45–54	1569 (52)	1616 (51)
55–64	1305 (55)	1095 (54)
65–74	1008 (60)	812 (57)
75–	430 (66)	747 (69)
All	6993 (54)	6402 (55)

Altogether, we analysed 13 395 serum samples for IgA-class tissue transglutaminase antibodies (Eu-tTG umana IgA, Eurospital S.p.A, Trieste, Italy) in 2001–02. The test used is based on an enzyme-linked immunosorbent assay technique (ELISA) with human recombinant tissue transglutaminase as antigen. Pooled estimates of the sensitivity and specificity of a human recombinant-based test have been reported to be 98% in adult populations.[2] Results are given in arbitrary units (AU) and the cut-off point for the test was 7.0 AU/mL according to instructions of the manufacturer. We further analysed tissue transglutaminase positive sera for IgA class endomysial antibodies using an indirect immunofluorescence method and a characteristic staining pattern at a serum dilution 1:≥5 was considered positive.[16, 17] Endomysial antibody-positive cases were considered to have unrecognized coeliac disease unless there was an earlier diagnosis of coeliac disease or dermatitis herpetiformis.

Due to the unexpectedly high percentage of tissue transglutaminase antibody positivity in sera in the Mini-Finland survey collected 22 years earlier, we also randomly selected 128 (one in 50) tissue transglutaminase antibody-negative serum samples and tested them for endomysial antibodies. In addition, to evaluate the stability of endomysial antibodies after long storage at −20 °C, we reanalysed 12 separate sera previously positive for IgA endomysial antibodies and drawn from biopsy-proven untreated coeliac disease patients an average of 14 (11 to 18) years earlier. The laboratory performing the reanalyses was blinded as regards the results of the primary analyses.

Total number of coeliac disease cases

In both cohorts, the total number of coeliac disease cases was obtained by adding together previously diagnosed coeliac disease and dermatitis herpetiformis patients and hitherto unrecognized screen-detected endomysial antibody-positive cases.

Statistical analysis

The analyses were performed using SAS 8.02 (SAS Institute, Cary, NC, USA) and SUDAAN 9.0.0 statistical software (Survey Data Analysis, Research Triangle Institute, Research Park Triangle, NC, USA),[18] which takes into account sampling weights and design effects. A logistic regression model was applied to estimate adjusted prevalences with 95% confidence intervals (CI) and odds ratios between the two surveys. In calculating the odds ratios, age, sex, educational level and survey were included in the models.[19] *P*-values were computed using Satterthwaite F-test and a value <0.05 was considered statistically significant.

RESULTS

Prevalence of previously diagnosed coeliac disease

The prevalence of diagnosed coeliac disease has increased substantially during the last two decades in Finland: only two ascertained coeliac disease cases had been diagnosed in 1978–80 (clinical prevalence of 0.03%, 95% CI 0–0.07) compared to 32 (0.52%, 95% CI 0.35–0.68) in 2000–01.

Prevalence of unrecognized coeliac disease

In the Mini-Finland survey (1978–80), altogether 578 (8.27%) out of all the 6993 analysed serum samples were tissue transglutaminase antibody-positive (median value 8.4 AU/mL, lower quartile 7.5, upper quartile 10.0, range 7.1–25.0); 12.80% (74, 53 females) out of 578 tissue transglutaminase-positive samples were also endomysial antibody-positive (Figure 1). The prevalence of unrecognized coeliac disease was thus 1.03% (95% CI 0.79–1.27). None of the 128 randomly selected tissue transglutaminase-negative samples was endomysial antibody-positive.

In the more recent population cohort (2000–01), tissue transglutaminase antibody positivity was found in

129 (2.02%) of the 6402 serum samples analysed (median value 16.2 AU/mL, lower quartile 9.9, upper quartile 21.0, range 7.1–26.0). The number of unrecognized coeliac disease cases with positive endomysial antibodies was 92 (57 females), yielding a screen-detected prevalence of 1.47% (95% CI 1.17–1.77). The age- and sex-adjusted odds ratio for the prevalence of unrecognized coeliac disease between the two study cohorts was 1.45 (1.06–1.99).

In all 12 separate sera drawn from biopsy-proven untreated coeliac disease patients up to 18 years earlier, the endomysial antibody result remained positive.

Total prevalence of coeliac disease

The total prevalence of coeliac disease increased in a statistically significant manner from 1.05% (two previously diagnosed + 74 unrecognized coeliac disease cases out of 6993 subjects) in 1978–80 to 1.99% (32 + 92 out of 6402) in 2000–01 (Table 3). The age- and sex-adjusted odds ratio for prevalence between the two study cohorts was 1.94 (95% CI 1.44–2.60). After further adjustment for educational level, the odds ratio was 1.56 (95% CI 1.12–2.18). The age-adjusted total prevalence increased from 0.65% (95% CI 0.41–0.89) to 1.65% (95% CI 1.16–2.14) in men and from 1.40% (95% CI 1.05–1.75) to 2.29% (95% CI 1.78–2.80) in women. The total prevalence of coeliac disease increased in a statistically significant manner in the age-groups 30–44 and 45–54 and the increasing trend could also be seen in older age-groups (Table 3). In addition, screening revealed that as many as 97% (74 out of 76) of coeliac disease cases were unrecognized in 1978–80 and 74% (92 out of 124) still in 2000–01.

Table 3. Total prevalence of coeliac disease in 1978–80 and 2000–01 according to age

Age (Years)	The total prevalence of coeliac disease, %* (95% Confidence intervals) Mini-Finland year 1978–80	Health year 2000–01	*P*-value
30–44	1.06 (0.69–1.43)	1.87 (1.28–2.46)†	0.01
45–54	1.27 (0.68–1.86)	2.41 (1.57–3.25)†	0.03
55–64	1.28 (0.71–1.85)	2.20 (1.30–3.10)	0.08
65–74	0.84 (0.31–1.37)	1.68 (0.86–2.50)	0.1
75–	0.28 (0–0.83)	1.21 (0.35–2.07)	0.18
All	1.05 (0.80–1.29)	1.99 (1.64–2.33)†	0.004

* Sex-adjusted prevalences with 95% confidence intervals were estimated by a logistic regression model. Both earlier diagnosed coeliac disease patients and screen-detected endomysial antibody-positive cases were included in the prevalence figures; † The difference between the surveys is statistically significant.

DISCUSSION

The findings here indicate for the first time that the total prevalence of coeliac disease has increased in the course of time. In Finland, it almost doubled during the time-span examined, being 1.05% in 1978–80 and 1.99% in 2000–01, and the increase could be seen in both sexes and different age-groups. We took advantage of two large adult-representative population-based cohorts. The outstanding participation rates, the similar sampling and serological testing methods and the uniform diagnostic criteria for both cohorts greatly strengthen the validity of our conclusions.

We based the definition of unrecognized coeliac disease on positivity for serum endomysial antibodies without small-bowel biopsy, as has previously been done in large screening studies in USA and Europe.[6, 8, 9] The test used here has been standardized and validated in Europe,[17] and its specificity has been repeatedly reported to approach 100%.[2] Theoretically, there is a possibility of false-positive cases in both cohorts. In practice, the finding of a real false-positive case is most probably a rarity for the following reasons. The patchiness of mucosal pathology may wrongly lead to exclusion of coeliac disease and a so called false endomysial antibody-positive case in fact indicates false-negative histology.[2] In addition, endomysial antibody positive cases with normal villous structure often evince villous atrophy and crypt hyperplasia later in life.[20, 21] These patients without manifest mucosal lesion may even be gluten-sensitive, with a favourable response to gluten-free diet.[22–28] Furthermore, a high concordance between endomysial antibody positivity and the coeliac type HLA-genotype, i.e. DQ2 or DQ8, has been clearly shown regardless of small-intestinal mucosal histology.[7, 20, 29] As pooled sensitivity of endomysial antibodies has been reported to be 90% in adults,[2] we cannot exclude the possibility that there were some endomysial antibody-negative coeliac disease cases in both cohorts. In such a case, our prevalence figures may even slightly underestimate the true prevalence at the defined time-points.[30]

We detected a surprisingly high frequency of tissue transglutaminase antibody positivity in the old sera collected in 1978–80. Tissue transglutaminase antibodies were not used in calculating the prevalence of coeliac disease, as this hardly represents the true prevalence of unrecognized coeliac disease in this study. As to the fact that tissue transglutaminase antibody tests have earlier yielded positive results in chronic liver and heart diseases without concomitant coeliac disease,[31, 32] the most likely explanation is the concentration of old sera, resulting in an increased optical density in the ELISA method, many low positive cases and hence a high positivity rate. Besides, to ascertain that most if not all unrecognized coeliac disease cases were among the tissue transglutaminase antibody-positive subjects, we randomly tested one in 50 tissue transglutaminase-negative individuals and showed that none was endomysial antibody-positive. In addition, long-term storage at −20 °C does not seem to affect sensitivity of IgA endomysial antibodies, as all separate sera drawn from biopsy-proven untreated coeliac disease patients with no severe symptoms up to 18 years earlier remained positive. It is also unlikely that sensitivity had declined because of decreased endomysial antibody titre during the storage, as in contrast, the proportion of tissue transglutaminase antibody positive cases was high defined from the same stored sera; both tissue transglutaminase and endomysial antibody tests measure the same autoantibody of sera by a different method. Still, endomysial antibody titres of the 1978–80 cohort were basically high supporting the stability of antibodies during the storage (data not shown). The stability of serum autoantibodies after long-term storage at −20 °C has also been shown in previous studies.[33, 34] Hence, the lower prevalence of coeliac disease in 1978–80 compared to 2000–01 is hardly likely to be because of loss of activity of antibodies during storage. Instead, if the concentration of the old stored sera had increased endomysial antibody titres, the prevalence of unrecognized coeliac disease in 1978–80 would have been overestimated in our study and the difference in the total prevalence between the two cohorts would be greater than reported.

During the study period, clinically diagnosed biopsy-proven coeliac disease cases increased many-fold. The prevalence figures for diagnosed coeliac disease of 0.03% in 1978–80 as against 0.52% in 2000–01 are fully concordant with previous Finnish prevalence studies.[3, 35] The rise in the prevalence of diagnosed coeliac disease is very likely due to ascertainment; a greater awareness of the disease, the increased use of serologic screening tests and good availability of open access endoscopy with routine small-bowel biopsy.[3, 4] Regardless of the better detection rate, 74% of coeliac disease cases still went unrecognized in 2000–01 and the finding of these cases remains a diagnostic challenge for clinicians. On the other hand, the need to diagnose all coeliac disease cases has to be proven in future studies concerning the prognosis of the disease.

In addition, we also found a statistically significantly increased prevalence of unrecognized coeliac disease (1.03% compared to 1.47%), as the 95% confidence intervals of the age- and sex- adjusted odds ratio between the study cohorts were above one. We wish to stress that the ratio of known to unrecognized coeliac disease cases varies over time and between different districts due to varying diagnostic activity. However, a changing detection rate does not influence the sum of recognized and unrecognized coeliac disease cases. Thus, if the total prevalence of coeliac disease had remained the same during the study period and diagnosed coeliac disease had increased statistically significantly as previously stated, the prevalence of unrecognized coeliac disease should have decreased instead of increasing.

The main message of the present finding is that the total prevalence of coeliac disease has increased significantly and nearly doubled during the last two decades. We carried out a novel study in coeliac disease and thus, the comparison of this result with previous studies on the same issue is impossible. However, a steady rise in the incidence of type 1 diabetes, other autoimmune diseases such as multiple sclerosis and Crohn's disease, and allergic diseases has been noted in developed countries over the last few decades.[10] The observed rising trend in coeliac disease is parallel to that seen in type 1 diabetes in Finland (Figure 2).

Such a rapid change in disease frequencies cannot be attributed to genetic changes in the population but rather to environmental factors.[36] The reasons for such a remarkable increase in morbidity are largely unknown. According to the hygiene hypothesis the main factor underlying the increased prevalence of autoimmune diseases is the reduction in the incidence of infectious diseases. An early childhood infection or normal establishment of indigenous intestinal microbiota could down-regulate immunity and suppress different autoimmune disorders.[10, 36, 37] So far, research

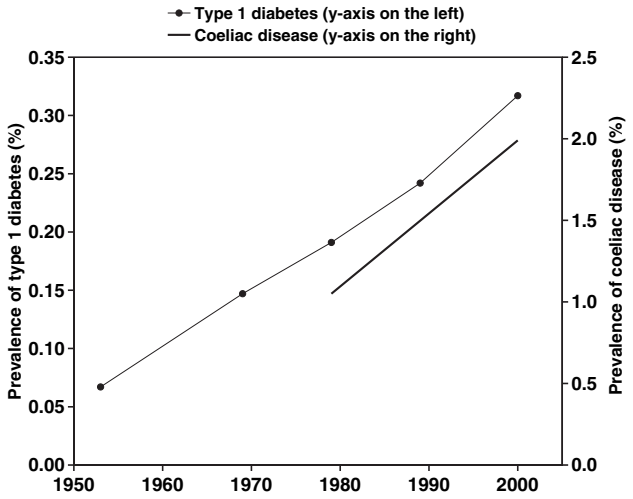

Figure 2. Increasing prevalences of coeliac disease and type 1 diabetes over time in Finland. Prevalences of both diseases have nearly doubled during the last two decades. Data derived from Somersalo,[43] Reunanen *et al.*[44] and the national register of the Social Insurance Institution of Finland.

in the field of environmental factors affecting coeliac disease has focused on infant feeding practices. The best available evidence suggests that introducing gluten in small amounts at 4 to 6 months of age while still breastfeeding might protect from coeliac disease, but the results of the studies in question are still inconclusive.[38–41] On the other hand, such changes in infant dietary practices might merely delay the clinical manifestation of coeliac disease and not inhibit the underlying process resulting in the small-intestinal coeliac lesion.[38, 41] The doubled prevalence of the disorder might also be due to increased amounts of gluten in the diet after infancy.[42] According to the background information (Table 1), the most significant difference between the cohorts was the improvement in educational level over time. After adjusting for educational level, the difference between the cohorts slightly decreased but remained statistically significant, indicating that the possible aetiological factors may be both independent of and associated with education and higher socio-economic class.

As we compared two cross-sectional studies, it is necessary to discuss possible period and cohort effects. To minimize the effect of the changed diagnostic activity, we added together both diagnosed and unrecognized coeliac disease cases in calculations of the total prevalence of coeliac disease. However, it is likely that the change in the total prevalence of coeliac disease is due to some periodic or continuous environmental factors. As regards to cohort effect, we can of course not ascertain that mortality of coeliac disease population had remained the same over time. Cohort effect might partly explain our results in case that more coeliac disease cases had died before the sampling in the earlier cohort compared to the later cohort. However, a dramatic change in mortality of coeliac disease population is unlike over 20 years of follow-up and hardly explains our results.

In conclusion, the total prevalence of coeliac disease has increased considerably in Finland in the course of time. This cannot be attributed to the better detection rate and must thus reflect a true rise in the prevalence of the disorder. Identification of the environmental factors responsible for the increased frequency of coeliac disease constitutes an important issue for further studies.

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