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Alimentary Tract

Celiac disease diagnosis still significantly delayed – Doctor's but not patients' delay responsive for the increased total delay in women

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ABSTRACT

Background: There is insufficient data on diagnostic delay and associated factors in celiac disease (CeD) as well as on its potential impact on the course of disease.

Methods: Specifically taking its two components – patients' and doctors' delay – into account, we performed a large systematic patient survey study among unselected CeD patients in Switzerland.

Results: We found a mean/median total diagnostic delay of 87/24 months (IQR 5–96), with a range from 0 up to 780 months and roughly equal fractions of patients' and doctors' delay. Both mean/median total (93.1/24 vs. 60.2/12, $p < 0.001$) and doctors' (41.8/3 vs. 23.9/2, $p < 0.001$) diagnostic delay were significantly higher in female vs. male patients, whereas patients' delay was similar, regardless of preceding irritable bowel syndrome diagnosis. Patients with a diagnostic delay shorter than 2 years were significantly less often in need of steroids and/or immunosuppressants, substitution for any nutritional deficiency but more often free of symptoms 6 and 12 months after diagnosis.

Conclusions: There is a substantial diagnostic delay in CeD, which is associated with a worse clinical outcome and significantly longer in female patients. This increased diagnostic delay in women is due to doctors' but not patients' delay and cannot be explained by antecedent IBS prior to establishing the CeD diagnosis.

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1. Introduction

Celiac disease (CeD) refers to a chronic immune-mediated disease with intestinal and systemic manifestations, triggered by gluten ingestion in persons with a genetic susceptibility [1]. Once considered a rare childhood disease until the late 1970 [2], CeD has emerged to be among the most abundant genetically based diseases. According to newer investigations based on serologic

screening a tenfold increase in estimated prevalence of up to 1% in Europe and the U.S. can be observed [2–4]. There is a shift in baseline patient characteristics from classical symptoms of CeD including diarrhoea and malabsorption (classical CeD). Nowadays, an increasing number of patients are diagnosed lacking these classical clinical features with rather atypical symptoms, such as iron deficiency or by chance, which is more common in elderly [5] patients (silent or atypical CeD) [6,7].

Several investigations point to a considerable diagnostic delay from onset of the first symptoms until the diagnosis is finally established. Most of these studies have found a total delay in the range between 9 and 12 years [5,8,9]. Likewise, it has been shown, that it takes a considerable number of physician visits [10,11] until establishing a diagnosis of CeD, even with typical symptoms at

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presentation and even in case of a gastroenterologist being the primary physician addressed [9]. Although some [8,12] (but not all [5]) studies indicate a decrease in its magnitude in recent years, the diagnostic delay and eventually under-diagnosis of CeD remains an important issue. Total diagnostic delay can be deconstructed into two portions: a patient- and a doctor-derived component, referring to the timespan from onset of first CeD symptoms until consulting a physician and from this first physician visit until diagnosis of CeD, respectively.

The magnitude of diagnostic delay appears to directly translate into clinical impairment in patients with unrecognised CeD. After receiving their diagnosis, quality of life improves in nearly four out of five patients [9] despite restrictions and inconveniences related to gluten free diet (GFD), which is a factor known to potentially impair social function scores [13]. This undermines the importance of timely establishing the diagnosis. However, diagnostic delay in CeD not only reduces patients' quality of life before diagnosis [8] but also may impact on associated complications, such as osteoporosis [11] as well as medical costs, which tend to decrease after CeD diagnosis [14]. Particularly worrying are indications of an increase in mortality associated to diagnostic delay [15,16], even in latent CeD patients [17].

Currently, our knowledge regarding diagnostic delay in CeD remains scarce. Specifically, risk factors for patients' and doctors' delay have not been sufficiently clarified. In a small survey study from Germany no differences in diagnostic delay were found in male vs. female patients, however only including 80 male patients [18]. In contrast, according to a nationwide study from Finland including some 800 patients a longer diagnostic delay in women was suggested [12]; however, patients' and doctors' delay were not distinguished. To the best of our knowledge, currently no large scale investigations of factors associated with total, patients' and doctors' diagnostic delay in CeD are available. We therefore aimed to address these open questions in a large nation-wide questionnaire study in an unselected CeD population.

2. Material and methods

2.1. Questionnaire and patients

A questionnaire (Supplementary Table 1) covering amongst others baseline characteristics, CeD diagnosis, medical history including symptoms and complications, quality of life (QoL) and medication use was sent to all members of the IG Zöliakie, the CeD patient common interest group in Switzerland. The questionnaire specifically aimed at obtaining information regarding the diagnostic process and potential delays, such as type and duration of symptoms prior to the first visit to a physician and interval until the final diagnosis of CeD was established (including the year and if available exact months of these points in time). The need for a formal ethical approval process was waived by our local Ethics Committee (KEK Zurich, Switzerland) due to anonymised data collection. For each patient we calculated a total diagnostic delay (the entire interval from the first occurrence of symptoms until the diagnosis celiac disease was finally established) comprising the sum of patients' delay (i.e. the timespan between first occurrence of symptoms until first consultation of a physician) and doctors' delay (i.e. the timespan between this first physician visit and establishment of CeD diagnosis).

2.2. Statistical analysis

All collected data was anonymised and entered into a database. Data distribution was analysed using Normal-QQ-Plots and D'Agostino and Pearson omnibus test with regards to normal

distribution. Results of quantitative data are presented as median plus interquartile ranges (IQR) for nonparametric data or mean \pm SD and range for parametric data, whereas categorical data are summarised as the percentage of the group total. The Mann-Whitney test was used to analyse nonparametric quantitative data and to evaluate whether diagnostic delay was different between distinctive subgroup of patients. Chi-Square testing was applied to test for difference among categorical variables.

Binary Logistic regression analysis was used to further evaluate diagnostic delay (total, patients' and doctors', respectively) as dependent variable with potential associated factors applying stepwise regression modelling. Long diagnostic delay was defined according to the 75% percentile of the time interval, i.e. when 75% of patients had their first physician's visit or been diagnosed after symptoms began for patients' and total delay, respectively or been diagnosed after first seeing a doctor for their symptoms for doctors' delay. We evaluated the following independent variables (including the binary description of the variable): sex (male vs. female), age at diagnosis of CeD (≤ 30 vs. >30), body mass index (BMI, i.e. body weight in kg divided by body size in metres in square; ≤ 25 vs. >25), family history (relative i.e. either first, second or third degree, with CeD; no relative vs. relative(s) with the disease), smoking (non-smoker vs. smoker at time of responding the questionnaire), antecedent irritable bowel syndrome (IBS; i.e. a diagnosis or suspicion of IBS prior to establishing CeD diagnosis; no IBS vs. IBS) and the year of diagnosis of CeD (up to 2009 vs. 2010 and thereafter). Primarily, the potential risk factors for long delay were each tested separately (univariate analysis). In a second step, all risk factors with $p < 0.2$ were combined in a binary multivariate logistic regression model, separate for total, patients' and doctors' delay.

The statistical analyses were performed using SPSS (Version 21; IBM, Armonk, NY, USA) and Prism (version 6, GraphPad Software, La Jolla, CA, USA).

3. Results

3.1. Characteristics of the study population and diagnostic delay in the overall patient cohort

A total of 3800 questionnaires were mailed to CeD patients associated to the Swiss CeD patient interest group (IG Zöliakie). 1689 questionnaires were returned and could be analysed, equalling to a response rate of 44.4%. Important baseline characteristics of the cohort are depicted in Table 1.

Across our cohort of CeD patients we found a mean/median total diagnostic delay of 87/24 months (IQR 5–96) with a range from 0 up to 780 months. The proportion of the patient- and physician-derived components of the total diagnostic delay were of similar magnitude with a mean/media patients' and doctors' delay of 40.8/2 (IQR 0–24) and 37.9/3 (IQR 0–24) months, respectively (Fig. 1, upper row).

3.2. Diagnostic delay and gender

We investigated potential differences of diagnostic delay and its two components according to gender. As shown in Table 1 we did not observe any significant differences in baseline characteristics according to gender aside from preceding IBS (as shown below) as well as a slightly higher body mass index (BMI) in men compared to women. Of special note, neither age, age at diagnosis nor year of diagnosis differed between female and male CeD patients. Both total and doctors' diagnostic delay were significantly higher in women vs. men with mean/median values of 93.1/24 vs. 60.2/12 ($p < 0.001$) for total 41.8/3 vs. 23.9/2 ($p < 0.001$) for doctors' delay.

Table 1
Baseline patient characteristics.

Sex	371 male (22%), 1284 female (76%), 34 unknown (2%)	
Current smoking status ^a (overall/men/women)	7.8/7.3/7.8%	n.s.
Having a 1st, 2nd or 3rd degree relative with CeD (overall/men/women)	35.2/35.0/35.4%	n.s.
Antecedent IBS (overall/men/women)	15.3/10.5/16.7%	p = 0.004
Typical symptoms ^b of CeD prior to diagnosis (overall/men/women)	84.7/83.3/85/4%	n.s.
Mean age (overall/men/women)	41.3/40.7/41.6 years Range: 0–92/1–92/0–82 years	CI (95%) 7.5–73.7/5.8–76.5/8.1–72.9; n.s.
Mean age at diagnosis (overall/men/women)	31.1/31/31.2 years Range: 0–83/0–83/0–83 years	CI (95%) 1.5–63.9/1.6–66.9/1.4–63.2; n.s.

Baseline characteristics regarding important variables associated to CeD diagnosis and diagnostic delay are shown for the cohort overall as well as separated according to sex. *p*-Values for significant differences according to sex are given, when applicable (n.s. = not significant).

^a At the time of taking part in the survey study.
^b According to the Oslo definition 2012, [37].

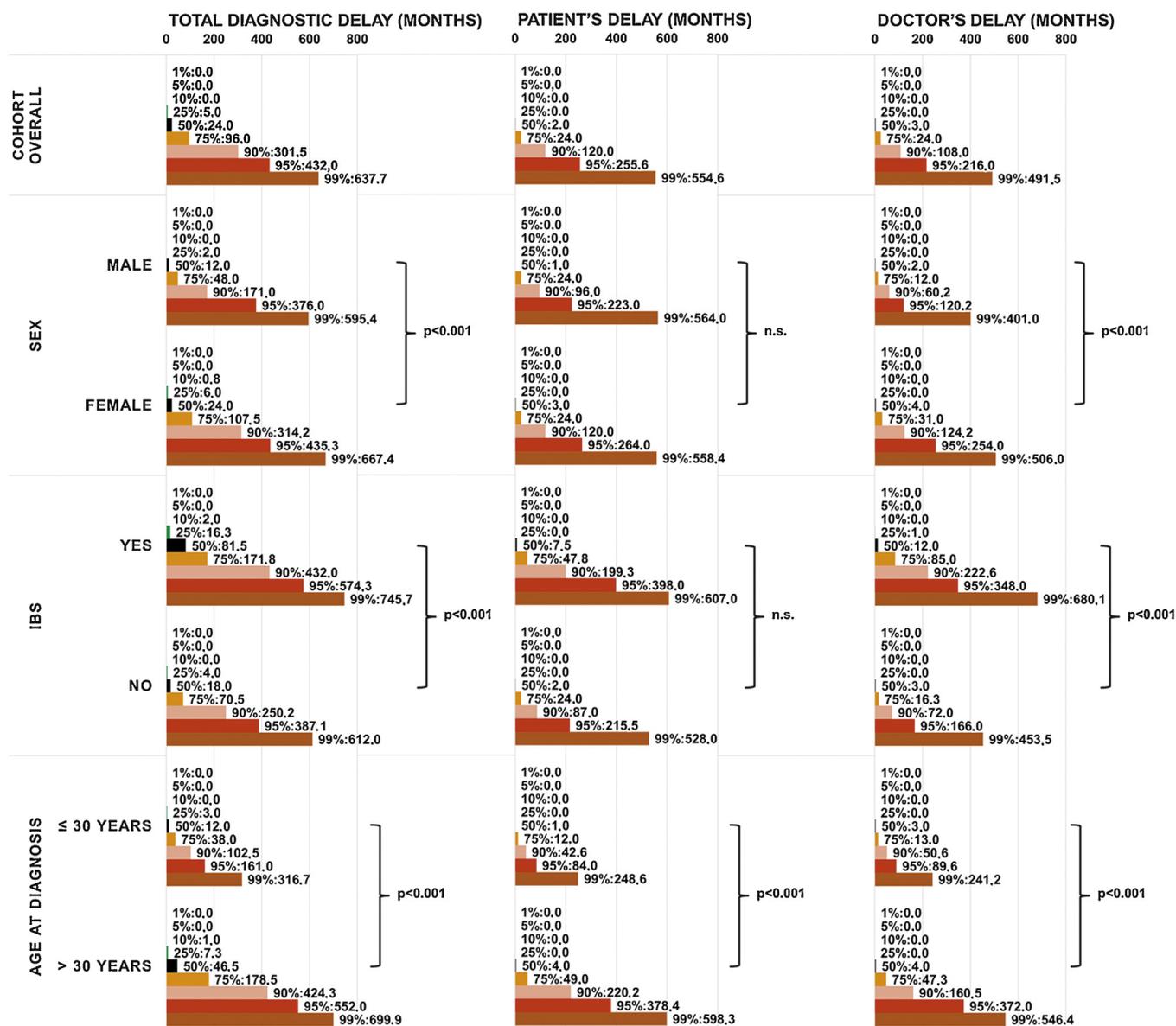


Fig. 1. Diagnostic delay overall and according to subgroups. The 1, 5, 10, 25, 50, 75, 90, 95 and 99 percentile of the total diagnostic delay (left column) as well as patients' (middle column) and doctors' (right column) are shown for the cohort overall as well as according to the subgroups sex, presence of IBS and age at diagnosis. Both total diagnostic delay and doctors' delay are significantly higher in women, patients with IBS and aged >30 years at diagnosis, while patients' delay is similar regarding sex and IBS with differences only regarding age at diagnosis.

Table 2
Univariate and multivariate analysis of factors associated with diagnostic delay.

Factor	Univariate			Multivariate		
	Total	Patients'	Doctors'	Total	Patients'	Doctors'
Age At Diagnosis (≤ 30 vs. >30)	OR 5.0 ($p < 0.001$; CI 3.8–6.7)	OR 2.3 ($p < 0.001$; CI 1.8–2.9)	OR 2.0 ($p < 0.001$; CI 1.6–2.5)	OR 4.6 ($p < 0.001$; CI 3.4–6.2)	OR 2.1 ($p < 0.001$; CI 1.6–2.7)	OR 1.9 ($p < 0.001$; CI 1.4–2.4)
Sex (male vs. female)	OR 1.8 ($p < 0.001$; CI 1.3–2.5)	OR 1.2 (n.s., $p = 0.476$; CI 0.8–1.5)	OR 1.7 ($p = 0.001$; CI 1.2–2.3)	OR 1.8 ($p = 0.001$; CI 1.3–2.6)	–	OR 1.5 ($p = 0.009$; CI 1.1–2.1)
BMI (≤ 25 vs. >25)	OR 1.3 ($p = 0.048$; CI 1.0–1.8)	OR 1.2 (n.s., $p = 0.295$; CI 0.9–1.6)	OR 1.2 (n.s., $p = 0.235$; CI 0.9–1.7)	OR 0.9 (n.s., $p = 0.690$; CI 0.7–1.3)	–	–
Relatives with CeD (no relatives vs. relatives)	OR 1.6 ($p < 0.001$; CI 1.3–2.0)	OR 1.3 ($p = 0.018$; CI 1.1–1.7)	OR 1.2 (n.s., $p = 0.241$; CI 0.9–1.5)	OR 1.7 ($p < 0.001$; CI 1.3–2.2)	OR 1.4 ($p = 0.014$; CI 1.1–1.8)	–
Smoking (no Smoking vs. Smoking)	OR 1.0 (n.s., $p = 0.911$; CI 0.6–1.5)	OR 1.40 (n.s., $p = 0.124$; CI 0.9–2.1)	OR 1.0 (n.s., $p = 1.0$; CI 0.6–1.5)	–	OR 1.1 (n.s., $p = 0.799$; CI 0.7–1.6)	–
IBS (no IBS vs. IBS)	OR 3.0 ($p < 0.001$; CI 2.2–4.0)	OR 1.6 ($p = 0.002$; CI 1.2–2.2)	OR 2.7 ($p < 0.001$; CI 2.2–4.0)	OR 2.7 ($p < 0.001$; CI 2.0–3.8)	OR 1.6 ($p = 0.004$; CI 1.2–2.2)	OR 2.9 ($p < 0.001$; CI 2.1–3.9)
Year of Diagnosis (up to 2009 vs. 2010 and thereafter)	OR 0.6 ($p < 0.001$; CI 0.5–0.8)	OR 0.7 ($p = 0.024$; CI 0.62–1.0)	OR 0.6 ($p < 0.001$; CI 0.5–0.8)	OR 0.7 ($p = 0.026$; CI 0.5–1.0)	OR 0.8 (n.s., $p = 0.190$; CI 0.6–1.1)	OR 0.6 ($p = 0.001$; CI 0.5–0.8)

After separate testing of potential risk factors for total, patients' and doctors' delay (univariate analysis), all risk factors with a p -value < 0.2 were combined in multivariate analysis.

In contrast, patients' delay in women and men was similar (41.3/3 vs. 36.8/1, not significant, $p = 0.261$; Fig. 1).

3.3. Diagnostic delay and IBS

Female patients were significantly more often diagnosed with IBS prior to establishing CeD diagnosis (16.7 vs. 10.5% in women vs. men, $p = 0.004$). Patients with a formerly diagnosed or suspected IBS had a significantly longer total diagnostic delay than those without (mean/median 141.8/81.5 vs. 74.5/18 months, $p < 0.001$). Likewise, doctors' delay was significantly increased in this subgroup of patients (mean/median 71.3/12 vs. 30.6/16.3 months, $p < 0.001$). The numerical increase in patients' delay in patients with vs. without IBS did not reach statistical significance (mean/median 61/7.5 vs. 36/2, n.s.; $p = 0.052$, Fig. 1).

3.4. Diagnostic delay and IBS according to sex

In view of the longer diagnostic delay in women and patients with IBS as well as the higher percentage of CeD patients with antecedent IBS in women, the association of diagnostic delay with or without antecedent IBS according to sex was separately analysed. Similar to the overall cohort, both total and doctors' delay were significantly higher in women compared to men regardless of antecedent IBS with a mean/median total delay of 148.8/24 vs. 119.6/12 and doctors' delay of 97.9 vs. 4 vs. 65.9/2 months for women vs. men with IBS and 138.6/21 vs. 104.9/12 and 85.1/3 vs. 58.8/2 months in their counterparts without IBS. In contrast, patients' delay was not significantly different (mean median of 99.8/3 vs. 98.5/1 and 95.2/3 vs. 86.5/1 months in women vs. men with and without IBS, respectively, S-Figure 1).

3.5. Diagnostic delay and age at diagnosis as well as year of diagnosis

We next aimed to test for an association of patients' age at diagnosis and the time period of CeD diagnosis with diagnostic delay. Diagnostic delay was consistently shorter in patients diagnosed with CeD below the age of 30 compared to their counterparts diagnosed thereafter with a mean/median total delay of 35.9/12 vs. 132.7/46.5 ($p < 0.001$), patients' delay of 17/1 vs. 63.2/4 ($p < 0.001$) and doctors' delay of 18.5/3 vs. 55.5/4 ($p < 0.001$, Fig. 1).

Total diagnostic and patients' delay declined significantly from 1990 to 2009. However, no trend regarding doctors' delay over the same time period was obvious (S-Figure 2A). Differences in diagnostic delay in women vs. men remained intact in a subgroups analysis of all time periods with significant increased total as well as doctor's but not patient's delay, S-Figure 2B.

3.6. Univariate and multivariate analysis of factors associated with total, patients' and doctors' diagnostic delay

A multivariate analysis of factors associated with diagnostic delay identified age at diagnosis above 30 and antecedent IBS as risk factors for total, patients' and doctors' diagnostic delay above the 75-percentile. Year of diagnosis after 2009 correlated inversely with diagnostic delay (with the exception of patients' delay in the multivariate analysis, revealing only a numerical but not significant association). Female sex was significantly associated with longer total and doctors' delay both univariate and multivariate, while no significant association to patients' delay was seen. In the univariate analysis, a BMI above 25 kg/m² was a risk factor for a longer total diagnostic delay (but not patients' or doctors' delay). However, in the multivariate analysis no significant association was identified. We did not observe any significant association between diagnostic delay and smoking status (Table 2).

3.7. Clinical impact of diagnostic delay on the course of disease

We found a significant association of the total diagnostic delay on the likelihood of future freedom from any symptoms 6 and 12 months after diagnosis of CeD. Among patients who were diagnosed within a year after symptom development, 41.2% were asymptomatic after 6 months (58.8% after 12 months), whereas among the patients with a total diagnostic delay ≥ 1 year only 34.6% were free from symptoms 6 and 12 months after CeD diagnosis (52.7% after 12 months, $p = 0.011$ and 0.025 for freedom of symptoms 6 and 12 months after diagnosis, respectively). A similar difference was also seen comparing patients with a diagnostic delay smaller than two years compared to their counterparts with a longer diagnostic delay (Fig. 2A). In addition, patients were significantly less often in need of systemic steroids or immunosuppressive agents to treat CeD if their total diagnostic delay was below 2 years (Fig. 2B). The risk for deficiency states associated with CeD

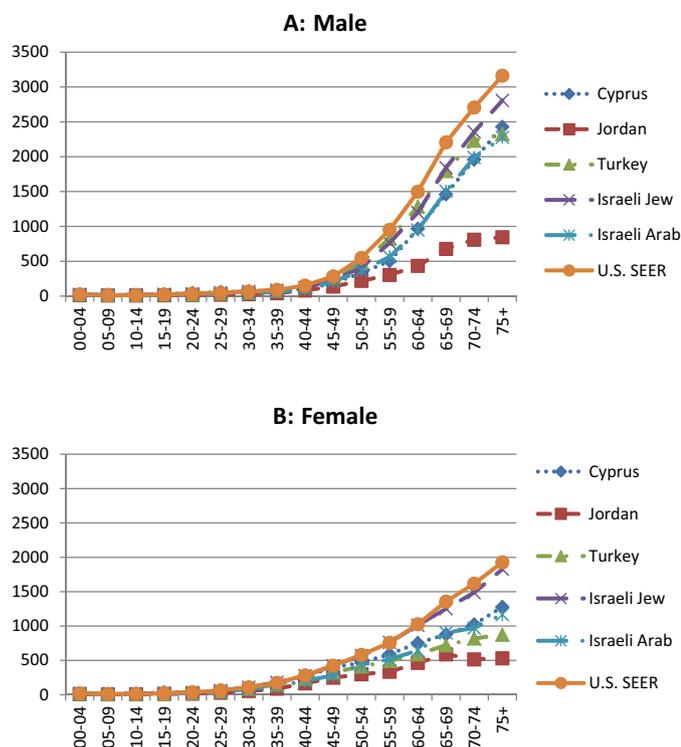


Fig. 2. (A–C) Diagnostic delay and course of disease. In (A) the probability of freedom from symptoms 6 and 12 months after diagnosis of CeD according to total diagnostic delay below two years vs. two years or more is depicted, while the percentage of patients ever in need of steroids or other immunosuppressive agents to treat CeD after receiving their diagnosis is shown in (B). The prevalence of nutritional deficiency states after receiving CeD diagnosis is shown in (C) for deficiency states overall as well as for individual deficiency states.

was significantly lower in patients with a diagnostic delay lower than 2 years compared to patients with a longer diagnostic delay for both, a composite of any deficiency state (RR 0.78, CI 0.72–0.84) as well as distinctive deficiency states, such as iron (RR 0.82, CI 0.73–0.92), vitamin B12 (RR 0.62, CI 0.52–0.74), vitamin D (RR 0.62, CI 0.53–0.72), vitamin E (RR 0.59, CI 0.48–0.72) and calcium (RR 0.42, CI 0.28–0.62; Fig. 2C).

The reported adherence rates to GFD were not different between patients with a short vs. long diagnostic delay (76.0%, 21.4%, 2.2% and 0.1% vs. 79.1%, 19.7%, 1.1% and 0% of patients stating that they were following always strict, always but with mistakes possible, sometimes and never a gluten-free diet, in patients with a delay ≤ 24 months vs. ≥ 24 months, respectively).

4. Discussion

Our study identifies a substantial diagnostic delay in CeD with a significant higher extent in women. This increase in delay in women vs. men has already been suggested previously [12]. However, this issue remained controversial according to the previous literature, as some studies did not identify any differences in terms of sex [8,18], while even an increased diagnostic delay in men has been suggested in a Finnish investigation [19]. Thus, the confirmation of an increased total diagnostic delay in women represents a crucial result of our investigation, contributing to resolve this controversy. In addition and more importantly, our analyses demonstrate, that—while both patient’s and doctor’s delay share about an equal importance in terms of the magnitude of the total diagnostic delay – this increased diagnostic delay in women vs.

men is nearly exclusively driven by a higher doctors’ delay, whereas patients’ delay seems to be similar across gender.

In our patient group the distribution of delay values is extremely skewed with a large fraction of patients with “low-range” values of less than 12 or 24 months and a small fraction with extensively long delays. Therefore, while noting pronounced differences between mean and median values in line with previous studies [8], we decided to provide both, median and mean values in the results section. The extent of total diagnostic delay in our CeD patients (mean: 7.25 years) may appear very high, yet is in line with previous reports [10–12]. Regarding doctors’ delay, in a study from Northern Ireland 40% of CeD patients had previously been referred to hospital with clinical symptoms up to 30 times before the diagnosis was established [10]. While the very high delay patients observed in our study appear perplexing, such extreme cases with a total diagnostic delay of at least 36 years in one study [20] and a delay of more than 10 years in a quarter of all investigated patients [20] have been described. Some studies even reported a mean delay of 11 [9] and 11.7 [5] years, respectively.

Our study identifies a prior diagnosis of IBS as a risk factor for a diagnostic delay. In a recent case control study from the UK a fourfold excess in IBS prevalence in CeD patients compared to a matched group without CeD was reported within the first year prior to CeD diagnosis [21]. These findings indicate a lack of consideration of CeD in a fraction of patients with CeD, especially in those with IBS-like symptoms. And the latter was found to be more prevalent in women. However, in our study, IBS increased the diagnostic delay in both, men and women, and the relative risk of antecedent IBS diagnosis between the short vs. long delay revealed no difference according to gender (odds ratio of IBS diagnosis of 0.334, 0.362 and 0.348 in men, women and CeD patients overall, respectively, in the short vs. long delay patients). As shown in S-Figure 1, the significant increase in doctors’ and total but not patients’ diagnostic in women was identified regardless of antecedent IBS diagnosis.

In total, only a minority of 15.3% of our patients were diagnosed with IBS prior to CeD diagnosis. A similar number has been reported in another study [21], where 16% of CeD patients had previously received an IBS diagnosis (compared to 4.9% in the control population). Similar to our study, there was an absolute excess of IBS diagnosis in CeD women vs. men but not a relative one. In view of these facts, diagnosis of or confusion with IBS at best partially explains the longer diagnostic delay in women. Diagnostic awareness of CeD in physicians performing upper gastrointestinal endoscopy does not seem to be lower for women, since duodenal biopsies were significantly less often obtained in men than in women [22]. One might thus speculate, that the discrepancy according to gender is related to the initiation of a proper evaluation and diagnostic testing in response to reported symptoms rather than specific testing for CeD once a medical evaluation has been initiated.

In our cohort, the mean age of diagnosis for men and women was similar (31.0 vs. 31.2 years). In other reports the majority of patients receive their diagnosis beyond the age of 30, most patients between 40 and 59 years [5,8], apparently with a slightly higher age in men [5,9]. In our study, the diagnostic delay was lowest after 2009, but no unanimous decrease in recent years could be detected (S-Figure 2B).

We could furthermore show a clear association between diagnostic delay and risk of nutritional deficiencies as well as more severe course of disease in terms of symptoms as well as need of immunosuppressants after diagnosis in our study. Such an adverse effect of longer diagnostic delay on future disease has been shown in a variety of medical conditions, such as for instance inflammatory bowel disease [23,24], psoriatic arthritis [25], eosinophilic esophagitis [26], ANCA-associated glomerulonephritis [27], Guillain-Barré Syndrome [28] or aortic stenosis [29]. As intuitively plausible,

quality of life (QoL) in unrecognised CeD was shown to be reduced, while after diagnosis and initiation of treatment QoL scores similar to or even better than the general population were achieved [8]. Our analyses point to a more benign cause of disease in patients with a diagnostic delay shorter than 2 years. One potential explanation might be a low health-seeking behaviour in some patients leading to both, diagnostic delay and low adherence to GFD after receiving the diagnosis. However, no signs of poorer adherence to GFD in the long-delay group of patients were detected in our cohort.

The fraction of patients having used steroids and/or immunosuppressants at least once in our cohort may appear surprisingly high (3.3% overall; 2% and 4.7% in those with a delay of <24 months and ≥24 months, respectively). Apparently, only in patients with true refractory CeD (RCD), i.e. the persistence of symptoms despite a verified straight adherence to GFD over more than one year and exclusion of differential diagnosis for villous atrophy, corticosteroids or other immunosuppressive agents are advocated in combination with nutritional support, although there is no evidence based standard treatment approach [30–32]. The literature on epidemiology of RCD in CeD is scarce with no available global data [30]. However, percentage of patients ever having been treated with steroids and/or immunosuppressants appears to be in the magnitude of cumulative RCD incidence according to a north American study, where 4.0% of patients revealed to have true RCD (1.5% in the principal centre in Boston) [33]. In addition, it appears perfectly plausible, that the use of steroids and immunosuppressants in our CeD cohort is somewhat higher as the cumulative incidence of true RCD, as physicians (potentially also driven by patient wish) might erroneously initiate corticosteroids or immunosuppressants in case of refractory CeD symptoms, when in fact a thorough review of dietary intake and potential differential diagnosis would represent the guideline-conform approach. Our study has the following strengths and limitations. In a retrospective questionnaire study the possibility of bias always remains including question design (ambiguous question or complex wording), sample match to population or inaccurate respondent's recall. However, investigations on patients' delay are virtually impossible to perform in a prospective manner and a study on this has to rely on patients' recall. In addition, it is unlikely that selective reporting of symptoms would be responsible for our findings, since women tend to report somatic symptoms more frequently, intensely and comprehensively compared to men [34], what would rather promote a more rapid diagnostic process and hence shorter diagnostic delay. Several factors underlying this sex discrepancy in symptom reporting have been implicated, including the socialisation process (and thus differences in acknowledging and disclosing any discomfort), differences in symptom labelling, description and reporting, differences in the prevalence of psychiatric disorders modulating the awareness towards somatic symptoms (such as anxiety and depression) as well as ultimately differences in somatic and visceral perception [34]. Our study is not population based but from people organised in a self-support group. However, dispersal of questionnaires via a patient organisation appears to be preferable in comparison to a distribution via treating physicians. In the latter case, coverage of patients would be less extensive as stable CeD patient do not frequently attend their physicians and our study would be at risk for pronounced referral centre bias (as physicians from larger institutions and academic hospitals tend to disproportionately contribute to recruitment). Our study is among the largest survey studies in CeD ever performed [5,9] and the high number of responders and the nationwide coverage of patients certainly is a strength.

While our large survey study is suitable to investigate factors associated with diagnostic delay and identify specific subgroups with an increased risk of longer delay, it cannot provide any explanations or derive definite conclusions with regards to

underlying reasons for discrepancies in patient's and doctor's delay. Accordingly, based on our results, we cannot provide any concrete recommendations on how to appropriately proceed to improve this situation. Evidently our findings on diagnostic delay in CeD underline the need for further research on this issue.

Underdiagnosis remains a crucial issue in CD, with about one in five or six patients (17%) ultimately having received their diagnoses according to a recent investigation from the US [35]. The magnitude of this dark figure of undiagnosed CD might be somewhat less pronounced in Europe but certainly still remain an important problem [19,36].

In conclusion, our study confirms a considerable diagnostic delay in CeD. Patients with a longer diagnostic delay are at increased risk for adverse outcomes including persistence of symptoms, nutritional deficiencies and need for immunosuppressants. Total diagnostic delay is significantly higher in patients over 30 years at diagnosis as well as female patients. We identify doctors' delay and not patients' delay as the driving force underlying this increase in total diagnostic delay in female patients. Our findings do not suggest that IBS is the major factor responsible for doctors' delay. Rather, our findings suggest the presence of a gender-dependent "genuine lack of awareness" [10] or at least reduced awareness for CeD in some physicians. Thus, our results, indicating a more favourable course of disease in patients with shorter diagnostic delay, in conjunction with the previous body of literature on course of disease and mortality certainly reinforce the need for an increased awareness for CD, especially in older patients, patients with symptoms suggestive for IBS and even more so in women.

Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.dld.2016.06.016>.

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