

Alimentary Tract

Anxiety and depression in caregivers of individuals with celiac disease – A population-based study



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ABSTRACT

Background & aims: Partner burden is common in celiac disease (CD), but it is unclear if parents of children with CD have increased burden, and if this may translate into depression and anxiety meriting healthcare. **Methods:** Nationwide population-based study of 41,753 parents and spouses (“caregivers”) to 29,096 celiac patients and 215,752 caregivers to 144,522 matched controls. Caregivers were identified from the Swedish Total Population Register, and linked to data on psychiatric disease in the National Patient Registry. Hazard ratios (HRs) for depression, anxiety, and (as a reference outcome measure) bipolar disorder were examined in a lifetime fashion but also in temporal relationship to date of CD diagnosis using Cox regression. A priori, we focused on parents of individuals diagnosed ≤ 19 years of age (children at the age of disease onset) and spouses of individuals diagnosed in adulthood, as such parents and spouses (“high-risk caregivers”) were most likely to live together with the patient at time of disease onset.

Results: On Cox analysis, depression was 11% more common in high-risk caregivers (HR = 1.11; 95%CI = 1.03–1.19) than in control caregivers while anxiety was 7% more common (HR = 1.07; 95%CI = 0.98–1.16). Combining anxiety and depression into a composite outcome measure, there was an 8% statistically significant risk increase (95%CI = 1.02–1.14). The highest excess risks for both depression and anxiety were seen just before and 4–8 years after the CD diagnosis. In contrast, bipolar disorder was not more common in caregivers to CD patients.

Conclusion: Caregivers to patients with CD may be at increased risk of severe burden.

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1. Introduction

Celiac disease (CD) is an immune-mediated disorder that occurs in about 1% of the Western population [1,2]. The disease is characterized by small intestinal inflammation with villous atrophy [3], and is triggered by gluten exposure in genetically predisposed individuals [4]. Treatment consists of a life-long gluten-free diet.

CD has been linked to a number of complications [4] including death [5]. Early reports by Hallert et al. [6] and Ciacci et al. [7] have also described a poor quality of life in patients with CD. While a fear of complications, a socially restrictive diet, and the need for regular

health check-ups may contribute to this diminished quality of life, other factors such as fatigue [8], depression [9], and even severe psychiatric disease [10,11] may also be important.

The concept of caregiver burden denotes increased stress due to primary illness in a relative [12]. Caregiver burden was first described in gastrointestinal disease in 2013, when Wong et al. demonstrated an increased burden amongst partners of patients with irritable bowel syndrome compared to controls [13]. Our group recently reported the findings from a similar study showing that more than a third of partners to CD patients suffer from at least mild-to-moderate burden [14]. A key limitation of this study was however the small sample size ($n = 94$ partners) and that patients and partners were recruited from a tertiary centre database. To examine the impact of CD on caregivers further, we linked nationwide data on patients with biopsy-verified CD in Sweden to data on

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Table 1
Characteristics of celiac and control first-degree caregivers (parents and spouses).

	From index individuals celiac diagnosis N		P-value
	Celiac FDRs	Control FDR	
Number, total	41,573	215,752	
High risk number, total	27,698	144,293	
Relation ^a			
Father	16,112	84,200	
High-risk fathers	10,214	53,956	
Mother	17,857	93,906	
High-risk mothers	10,328	54,948	
Spouse	7829	37,996	
High-risk spouse	7348	35,685	
Age group (birth year)			<0.01
–1939	10,811 (26%)	55,871 (26%)	
1940–1963	19,907 (48%)	106,960 (50%)	
1964–1986	10,839 (26%)	52,833 (24%)	
1987–2008	16 (0%)	88 (0%)	
Calendar year (study entry ^b)			0.31
–1989	5942 (14%)	31,046 (14%)	
1990–1999	16,974 (41%)	88,766 (41%)	
2000–2008	18,675 (45%)	95,940 (44%)	
Sex			0.15
Male	20,826 (50%)	107,245 (50%)	
Female	20,747 (50%)	108,507 (50%)	
Event (first diagnosis of depression)			
Father	430 (2.7%)	2012 (2.4%)	0.04
High-risk father	291 (2.8%)	1398 (2.6%)	0.14
Mother	656 (3.7%)	3329 (3.5%)	0.40
High-risk mother	449 (4.3%)	2093 (3.8%)	<0.01
Spouse	160 (2.0%)	686 (1.8%)	0.15
High-risk spouse	149 (2.0%)	635 (1.8%)	0.15
Total number of unique events	1236 (3.0%)	6022 (2.8%)	0.04
Total unique events in high-risk	883 (3.2%)	4121 (2.9%)	<0.01
Event (first diagnosis of anxiety)			
Father	303 (1.9%)	1438 (1.7%)	0.12
High-risk father	216 (2.1%)	1113 (2.1%)	0.74
Mother	561 (3.1%)	2730 (2.9%)	0.09
High-risk mother	400 (3.9%)	1906 (3.5%)	0.04
Spouse	112 (1.4%)	541 (1.4%)	0.59
High-risk spouse	107 (1.5%)	491 (1.4%)	0.59
Total number of unique events	975 (2.3%)	4701 (2.2%)	0.03
Total unique events in high-risk	722 (2.6%)	3503 (2.4%)	0.08
Follow-up time (years)			0.61
Median	10.9	10.9	
Range	0–41.5	0–41.6	
Sum, person-years of follow-up (1000 years)	506	2618	

^a The sum is greater than the total number since a patient can be both a parent and a spouse of 2 different CD patients.

^b Year of diagnosis of index individual with celiac disease.

more than 41,000 spouses or parents and examined the prevalence of depression and anxiety in these caregivers around the date of CD diagnosis.

2. Methods

2.1. Defining celiac cases and reference individuals (controls)

During 2006–2008, we contacted all Swedish pathology departments (n=28) to obtain data on small intestinal biopsies from the years 1969 to 2008 (Table 1). We requested data on personal identity number [15], date of biopsy as well as topography and morphology.

CD was defined as having villous atrophy (Marsh III) [16] on a small intestinal biopsy. Earlier validation has found that 95% of patients with villous atrophy in a Swedish setting have CD [17]. During the study period, 96% of adult gastroenterologists and 100% of surveyed paediatricians performed a small intestinal biopsy

before celiac diagnosis [17]. On average, three duodenal tissue samples were submitted per biopsy [18], and this should identify 95% of all CD [19]. In a blinded examination, Swedish pathologists correctly classified 90% of biopsies with VA [17]. The current study builds on the same dataset as our paper on mortality in CD [5].

For each individual with CD, the government agency Statistics Sweden identified up to five controls from the Swedish Total Population Register [20]. This register also contains data on first-degree relatives and spouses.

2.2. Relatives (parents and spouses)

In this study we examined depression and anxiety in parents and spouses of CD patients and their controls to see if caregivers to patients with CD show signs of burden of disease (as measured by having a diagnosis of either depression or anxiety). Further, we examined the temporal relationship of burden to CD diagnosis.

All parents and spouses who themselves had CD were excluded since caregiver burden is different in people who have the same disease. If an individual was recorded as a relative of two different index individuals we used the first high risk observation (defined later in the text), and if both observations were either high or low risk we used the first observation (date of the index individuals study entry) for our analyses, as bipolar disorders are unlikely to be triggered by a CD diagnosis in a relative and any excess risk here is would likely be due to surveillance bias of relatives.

2.3. Outcome measure

We used the national patient registry [21] to ascertain all registered diagnoses of depression (ICD-8: 296.0, 300.4; ICD-9: 296B, 300E; ICD-10: F32, F33) and anxiety (ICD-8: 300.0, 300.2, ICD-9: 300A, 300C, ICD-10: F40, F41) during follow-up. In addition, we added the two outcomes into a composite outcome measure (any depression or anxiety). We also modelled bipolar disorder (ICD-8: 296.1–3, 296.98–99; ICD-9: 295X, 296A, 296C–E; 296W; ICD-10: F30–31) as a reference control outcome measure.

2.4. Follow up time

We used several different models of time for our analyses. In our main analyses, time was modelled from date of the index individual's CD diagnosis until first registered outcome, death, first emigration or the 31st of December 2010, whichever occurred first. (In this analysis caregivers who had experienced depression or anxiety before the index individual's study entry date were excluded.) We also modelled yearly risk estimates (15 separate Cox regressions of the risk of outcome within the following year, the first regression starting from 5 years before the date of diagnosis of the index individual and the last regression starting 9 years after the diagnosis of the index individual, but individuals were still censored if death, first emigration or 31st December 2010 occurred within the year; people with previous events, however, were not censored at the start of each year).

2.5. Exposure

The exposure was defined as being a parent or spouse of an individual diagnosed with CD. Our main analyses were restricted to a subset of caregivers, "the high-risk group," defined as being either a parent of an index individual who received a CD diagnosis in childhood (age ≤ 19 years) or being a spouse of an individual diagnosed with CD in adulthood (age ≥ 20 years). We felt this represented a timeframe when the caregiver was expected to be living together with the index individual. Corresponding control caregivers served as the reference.

2.6. Covariates

Data on age and sex were retrieved from the Total Population Register.

2.7. Statistical analyses

We used Cox regression to estimate hazard ratios (HRs) adjusted for caregiver sex, age group, and calendar year of diagnosis (or study entry) of the patients with CD and their matched controls. Study entry for the original study cohort was defined as the date of CD diagnosis and corresponding date in matched controls. Covariates were modelled categorically (male vs. female, birth-year (1940–1963, 1964–1986, 1986– vs. –1939)) and calendar year of the index individual (–1989, 1990–1999 vs. 2000–2008).

In our main analysis we examined the hazard ratio and the absolute risk of a first diagnosis of depression, anxiety, and the

composite outcome for all high-risk caregivers. In two sensitivity analyses we set the outcome to be positive only when the diagnosis was coded as the main diagnosis or when the diagnosis occurred at least twice in the individual. Analyses for all caregivers (parents and/or spouses) and analyses stratified by relation (mother, high-risk mother, father, high-risk father, parents, high-risk parents, spouse and high-risk spouse) were also performed. Although anxiety and depression are not necessarily persistent (e.g. can recur with a new date of disease onset), it is still usual to have several registrations for the same episode; we therefore also modelled Cox regressions for yearly occurrence of the diagnoses from –5 until +10 years from diagnosis with the same adjustments as above. We also constructed descriptive figures of yearly disease occurrence (e.g. up to once per person and year) from 5 years before index diagnosis until 10 years after index diagnosis divided by the total number of observation years.

In a post-hoc analysis we adjusted for socioeconomic status of the index individuals with CD and their matched controls. While this is not a perfect measure of the socioeconomic status of the first-degree relatives we used it as a proxy since socioeconomic status is often similar within one family. We used the same socioeconomic classification as in our earlier paper [22].

In a second post-hoc analysis we also compared caregiver burden in celiac FDRs to a secondary comparison group consisting of 67,006 FDRs to individuals with gastrointestinal disease in the original control group. Gastrointestinal disease was defined as having a relevant ICD-code (ICD7: 532–553, 570–75, 578; ICD-8 and ICD-9: 520–566; ICD-10: K00–K63).

Statistical significance was defined as 95% confidence intervals (CIs) for risk estimates not including 1.0. We used SAS version 9.4 for all analyses.

2.8. Ethics

The current study was approved by the Ethics Review Board of Stockholm, Sweden. As per the decision of the review board, none of the study participants was contacted since the study was strictly registry-based [23].

3. Results

3.1. Background data

In total we identified 41,753 CD and 215,752 control caregivers, of whom 27,698 and 144,293 were classified as high-risk caregivers (Table 1). The median time of follow up was 10.9 years ranging from 0 to 41.6 years. More characteristics and crude number of events in every subgroup of the study population are available in Table 1.

3.2. Depression and anxiety parents or spouses

Depression was 11% more common in high-risk caregivers (HR = 1.11; 95%CI = 1.03–1.19, absolute risk 245 vs. 220 per 100,000 person-years) than in control caregivers while anxiety was 7% more common (HR = 1.07; 95%CI = 0.98–1.16, absolute risk 199 vs. 185 per 100,000 person-years). Combining anxiety and depression into a composite outcome measure, there was an 8% statistically significant risk increase (HR = 1.08; 95%CI = 1.02–1.14, absolute risk 383 vs. 353 per 100,000 person-years).

Restricting our individual outcomes to having psychiatric disease listed as the main diagnosis yielded similar estimates (depression: HR = 1.15; 95%CI = 1.06–1.24 and anxiety: HR = 1.10; 95%CI = 1.00–1.21, $p = 0.056$). When looking at the risk of repeated records of psychiatric disease (≥ 2 registered visits with either outcome), both depression (HR = 1.07; 95%CI = 0.98–1.18) and anxiety (HR = 1.05; 95%CI = 0.94–1.17) were more common in celiac care-

Table 2
Risk of outcome among different groups of caregivers. Numbers in bold are statistically significant.

	Depression	Anxiety	Composite outcome (anxiety or depression)
Risk first time ever diagnosis of outcomes from index individuals celiac diagnosis date (study entry date) adjusted for sex and age-group of the caregivers and the calendar year of the celiac diagnosis/study entry			
Fathers	1.12 (1.01–1.24)	1.09 (0.95–1.25)	1.09 (0.99–1.19)
High-risk fathers	1.09 (0.96–1.24)	1.00 (0.85–1.17)	1.03 (0.93–1.15)
Mothers	1.03 (0.95–1.12)	1.08 (0.98–1.19)	1.05 (0.98–1.13)
High-risk mothers	1.12 (1.02–1.25)	1.11 (0.99–1.24)	1.13 (1.04–1.22)
Parents	1.06 (0.99–1.13)	1.08 (1.00–1.17)	1.06 (1.01–1.12)
High-risk parents	1.11 (1.03–1.20)	1.06 (0.97–1.17)	1.09 (1.02–1.16)
Spouses	1.14 (0.96–1.35)	1.01 (0.81–1.25)	1.03 (0.89–1.19)
High-risk spouses	1.15 (0.96–1.37)	1.07 (0.85–1.34)	1.06 (0.91–1.22)
All caregivers (parents and spouses)	1.06 (1.00–1.13)	1.08 (1.00–1.16)	1.06 (1.00–1.11)
High-risk caregivers (parents + spouses)	1.11 (1.03–1.19)	1.07 (0.98–1.16)	1.08 (1.02–1.14)

givers, but for none of the outcomes was the association statistically significant.

3.3. Depression and anxiety: stratified analyses

The different categories of caregivers were also analysed separately. The risk of depression was significantly higher in all fathers, high-risk mothers and high-risk parents, whereas anxiety was only significantly increased when we analysed fathers and mothers together (“all parents”). Our composite outcome was significantly increased amongst high-risk mothers, all parents, high-risk parents and all caregivers (Table 2).

3.4. Bipolar disorder as a negative control

As caregiver burden is unlikely to induce bipolar disorder, we modelled the risk of bipolar disorder as a reference outcome measure. High-risk caregivers were at no increased risk of bipolar disease (HR = 0.95; 95%CI = 0.81–1.11).

3.5. Time trends

To model the time trends we calculated yearly HRs through 15 Cox regressions. Corresponding HRs and CIs were plotted in graphs (Fig. 1). We also modelled yearly occurrence of depression and anxiety as absolute risks (not adjusted for sex, age-group and calendar year of diagnosis) (Fig. 2). The graphs show that the risk of depression and anxiety is increased around two years before diagnosis and about 4–8 years after diagnosis, but not at time of diagnosis.

3.6. Post-hoc analyses

Adjusting for socioeconomic status of the index individuals with CD and their matched controls did not influence our risk estimates (HR for the composite outcome of anxiety and depression was 1.06 (95%CI = 1.00–1.11)).

Compared to FDRs of individuals with gastrointestinal disease, celiac FDRs were at decreased risk of anxiety (HR = 0.73, 95%CI = 0.67–0.80) and depression (HR = 0.73, 95%CI = 0.68–0.78).

4. Discussion

4.1. Main findings

Both depression and anxiety are more common in caregivers to patients with CD. Excess risks were seen especially a few years before diagnosis and 4–8 years after diagnosis. In contrast, there was no increased in bipolar disorder (which differs from major depression in their risk factors [24]) in caregivers to patients

with CD. While the caregiver burden was statistically significantly increased in celiac FDRs it was of borderline significance, and is unlikely to be specific for CD since the caregiver burden seems to be even higher in FDRs to individuals with other gastrointestinal disease.

4.2. Comparison with other studies

Our findings are consistent with our earlier study on partner burden [14]. That study used web-based interview questions to examine overall burden. Out of 94 partners, 34 (37%) reported at least mild-to-moderate burden resulting from the patient's diagnosis of CD [14]. In the current study, we specifically explored severe psychological burden in either partners or parents of CD patients. The proportion of caregivers with recorded psychiatric disease was naturally much lower (1236 (3.0%) and 925 (2.2%) of the 41,573 caregivers had a diagnosis of depression or anxiety, respectively (Table 1)). This translated into HRs around 1.1, signalling a small excess risk of both depression and anxiety in caregivers. However it should be noted that absolute excess risks were small (e.g. 25 extra cases of depression during 100,000 person-years of follow-up amongst CD caregivers), and that also relative risks were lower in caregivers than in patients themselves. As a comparison our earlier study on depression, also using registry-based data and Cox regression, found a 1.8-fold increased risk in patients with CD [9].

In our interview study, we noted that partner burden was largest in couples with relationship duration of at least 10 years [14]. In the current study, we were able to examine the temporal relationship between caregiver burden and date of celiac diagnosis. We speculate that the excess risk just before disease diagnosis may coincide with the onset of disease symptoms and initial disease investigation in the relative with CD. A second period with higher caregiver burden was seen 4–8 years after diagnosis. It is possible that receiving a celiac diagnosis may be accompanied by relief of having a diagnosis and therapeutic plan (“honeymoon period”), and the short-term challenges this disease implies (dietary modifications for the patient but often also for the caregiver(s)) are well tolerated. With time (4–8 years), however, worries for complications and prognostic uncertainties of a chronic disease in one's relative may impact the caregiver's well-being. In our previous study [14], in fact, these were the exact types of psychological burden that were most commonly reported by partners in long-term relationships. While we cannot rule out that the overall increased risk of depression and anxiety in parents mirrors shared genetic risk factors in patients with CD (who are at increased risk of psychiatric diseases themselves), this is less likely for spouses of CD patients who also demonstrated increased risk of psychiatric disease.

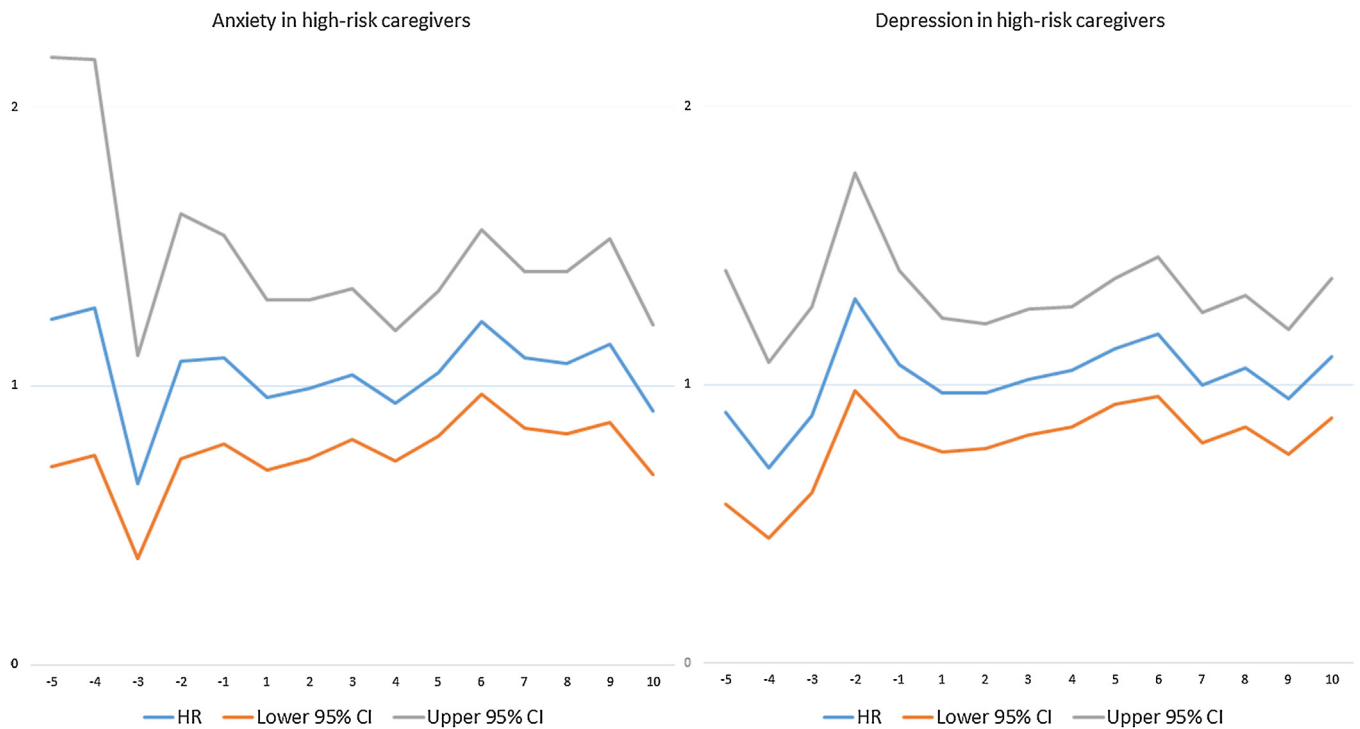


Fig. 1. Time-trends: yearly hazard ratios (HR) and confidence intervals (CIs) from Cox regressions around the time of diagnosis.

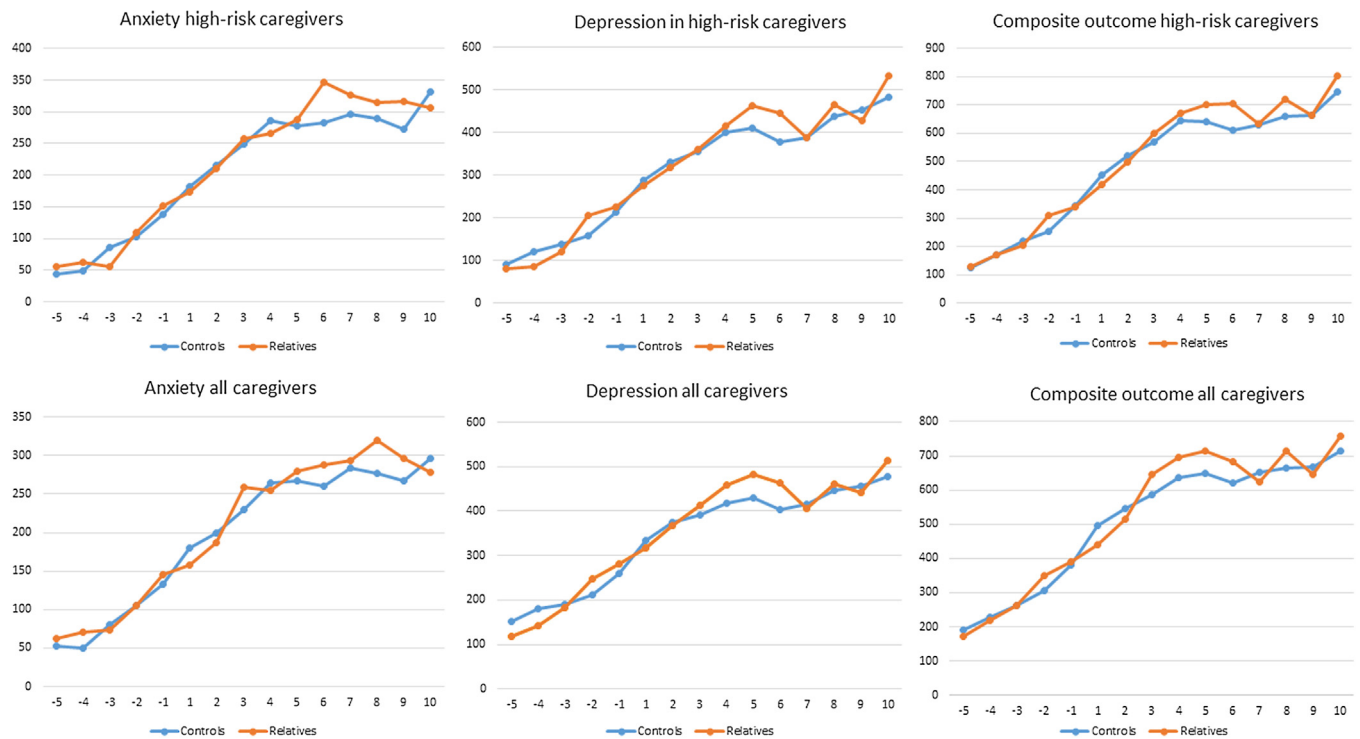


Fig. 2. Time-trends: yearly occurrence (absolute risk) of outcomes per 100,000 years of follow-up.

4.3. Strengths and limitations

We used histopathology data from all of Sweden's pathology departments to identify CD. Throughout the study period, small intestinal biopsy was the gold standard for diagnosis both in children and adults, and extensive validation has shown both a high sensitivity for diagnosed CD, as well as a high specificity (in fact,

villous atrophy has a higher positive predictive value for CD (95%) than having a physician-diagnosis of CD (86%) [25]). While we are unaware of any validation of depression and anxiety, most chronic diseases in the Patient Registry have a positive predictive value of 85–95% [21], with similar values for other psychiatric diseases. When Ekholm et al. reviewed medical records he found that 94/100 schizophrenia diagnoses were correct [26], and Grann et al.

reported that 92% of recorded personality disorders were correct [27].

The large number of patients, and consequently the large number of caregivers, means our study had great statistical power to detect also minor increased risk of severe burden. Importantly, we found around a 10% excess risk for both depression and anxiety. We were also able to examine fathers and mothers separately (little difference), as well as “high-risk parents,” where severe caregiver burden was most likely to be detected.

Finally our study was based on average patients. In our earlier study [14], older, female, well-educated white patients and partners with long-standing relationships dominated, and this may have an impact on the generalizability of the findings. Of importance is also the virtually complete recording of all inpatient and outpatient hospital-based healthcare in Sweden. This means that our study cannot suffer from “low participation rate” or biases related to participant characteristics.

This paper also has some limitations. We were unable to correlate our findings to dietary adherence in the patient. Dietary adherence seems to be associated with improved quality of life [28] (although data are inconsistent [29,30]), although we are unaware of its association to depression and anxiety in celiac patients. Furthermore, we had no information on sexual behaviour, which might otherwise influence caregiver burden. Sexual behaviour may be impaired in both patients with CD [31], and their partners (in our previous paper [14], 14% reported moderate-to-low sexual satisfaction, with a somewhat smaller percentage saying that CD interfered with their sexual activities). Neither did we have any data on symptom severity in CD. We relied on hospital-based diagnosis codes for the identification of depression and anxiety, which likely underestimated the incidence of these common conditions that do not always involve admission to hospital and sometimes not even medical encounters. Hence we cannot rule out that we have underestimated less severe depression and anxiety however, it is unlikely that such underestimation would be differential with regards to CD status. Finally we did not have access to data on medication (indicating potential psychiatric disease) in FDRs.

5. Conclusion

In conclusion, this study found a small increased risk of depression and anxiety in caregivers to patients with CD indicating that the effects of CD extends beyond the individual with the disease to other members of the family. Caregivers should take this into account and involve the whole family when interacting with a patient with CD.

Data sharing

No additional data.

Ethics approval

This project (2006/633-31/3) was approved by the Research Ethics Committee of the Karolinska Institutet, Sweden on June 14, 2006.

Conflicts of interest

None declared.

Author involvement

Study concept and design (JFL LE); acquisition of data (JFL); analysis and interpretation of data (LE); drafting of the manuscript (JFL

LE); critical revision of the manuscript for important intellectual content (JFL RA BL PHRG LE); statistical analysis (LE).

List of abbreviations

CD, celiac disease; CI, confidence interval; FDR, first-degree relative; HR, hazard ratio.

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