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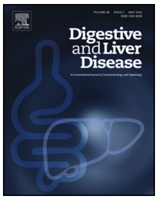

Alimentary Tract

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

Jonas F. Ludvigsson[a,b,c,d], Abhik Roy[d], Benjamin Lebwohl[a,d], Peter H.R. Green[d], Louise Emilsson[e,f,g,*]

[a] *Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden*
[b] *Department of Paediatrics, Örebro University Hospital, Örebro, Sweden*
[c] *Division of Epidemiology and Public Health, School of Medicine, University of Nottingham, Clinical Sciences Building 2, City Hospital, Nottingham, UK*
[d] *Department of Medicine, Columbia University College of Physicians and Surgeons, New York, NY, USA*
[e] *Department of Health Management and Health Economy, Institute of Health and Society, University of Oslo, Norway*
[f] *Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA*
[g] *Primary Care Research Unit, Vårdcentralen Värmlands Nysäter, Värmland County, Sweden*

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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 $\leq$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.

## 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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* Corresponding author.
*E-mail address:* lojsankik@hotmail.com (L. Emilsson).

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

| | From index individuals celiac diagnosis N | | |
|---|---|---|---|
| | Celiac FDRs | Control FDR | P-value |
| 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 patents 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.

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