Older age of celiac disease diagnosis and risk of autoimmune disease: A nationwide matched case-control study

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A R T I C L E   I N F O

Keywords:
Autoimmune disease  
Case-control  
Celiac disease  
Delayed diagnosis  
Gluten exposure

A B S T R A C T

Objectives: Celiac disease (CeD) has been linked to an increased risk of other autoimmune diseases, yet the impact of delayed CeD diagnosis on risk of developing additional autoimmune diseases remains uncertain. We investigated this through a nationwide matched case-control study.

Methods: Using the ESPRESSO cohort with histopathology data from Sweden’s 28 pathology departments, we assessed 46,575 biopsy-confirmed CeD cases from 1964 to 2017. We extracted 225,295 matched controls without histopathology information from the Swedish Total Population Register. Autoimmune disease was defined through diagnostic codes in the National Patient Register. Through conditional logistic regression we estimated odds ratio (OR) of autoimmune disease up until CeD diagnosis/matching date comparing CeD cases to controls across different age strata.

Results: A total of 3059 (6.6 %) CeD patients and 4076 (1.8 %) controls had earlier autoimmune disease. The overall OR for autoimmune disease in CeD was 3.50 (95%CI 3.32–3.70). The risk of autoimmune disease did not escalate with increasing age at CeD diagnosis. Compared with controls, the OR of autoimmune disease in CeD patients was 7.70 (95%CI 4.71–12.57) in those diagnosed with CeD in 0–4 years, 19.02 (95%CI 13.80–26.23) in 5–9 years, 6.18 (95%CI 5.14–7.44) in 10–14 years, 4.80 (95%CI 3.97–5.79) in 15–19 years, 4.24 (95%CI 3.55–5.07) in 20–29 years, 4.65 (95%CI 3.93–5.51) in 30–39 years, 3.67 (95%CI 3.30–4.09) in 40–59 years, and 1.67 (95%CI 1.50–1.85) in 60 years.

Conclusions: This study revealed an increased risk of autoimmune disease among CeD patients compared with controls. However, older age at CeD diagnosis did not seem to escalate the risk of autoimmune diseases.

1. Introduction

Celiac disease (CeD) is an immune response to gluten intake in individuals with a genetic susceptibility [1] and is recognized for its varied symptoms and related health issues [2]. A significant concern associated with CeD is its potential connection to other autoimmune conditions [3]. While it is clear that CeD is associated with an increased risk of a variety of autoimmune diseases [4–6], it is currently unclear if this is related to shared genetic or environmental factors, or if there is a causative relationship, where untreated CeD leads to increased autoimmune disease risk. While some studies have suggested that a delayed diagnosis of CeD, representing a prolonged duration of active CeD or gluten exposure, is associated with an elevated risk of autoimmune disease [7–10], other studies have not confirmed any such association [11–13]. The divergent findings have created ambiguity in understanding the implications of the age at which CeD is diagnosed and the risk of autoimmune diseases. Given that CeD afflicts more and more people worldwide [14], deciphering the association with autoimmune disease holds significant clinical relevance, as it can influence diagnostic approaches including potential population screening, patient management, and preventive strategies. To provide additional clarity on the impact of late CeD...
diagnosis on risk of autoimmune disease, we conducted a nationwide matched case-control study to investigate the association between the age of CeD diagnosis and the risk of autoimmune diseases.

2. Methods

2.1. Study population

This study was based on data from the nationwide ESPRESSO (Epidemiology Strengthened by histoPathology Reports in Sweden) cohort (Fig. 1) [15]. The ESPRESSO cohort, with 6.1 million biopsy records of the gastrointestinal tract gathered from all Swedish pathology departments (n = 28) between 1965 and 2017, with 2.1 million distinct individuals throughout Sweden [15]. The CeD diagnosis was based on the first presence of small-intestinal villus atrophy, classified under Marsh stage 3 based on snomed codes [16]. Notably, prior assessments have indicated that 95–99 % of Swedes exhibiting small-intestinal villus atrophy are confirmed cases of CeD [17, 18]. Subsequently, these CeD-diagnosed individuals were paired with up to five controls each from the Swedish Total Population Register. Matching was based on birth year, sex, county of residence, and calendar year at the diagnosis for cases and inclusion for controls. Furthermore, medical, demographic, and additional data, including educational details, for every participant included in the study were sourced from various Swedish national registers, including the National Patient Register (NPR, with inpatient records available from 1964 and hospital-based outpatient from 2001), the Total Population Register (TPR, accessible since 1968), and LISA (the longitudinal integrated database for health insurance and labor market studies, available from 1990). These datasets were linked together by the unique personal identity number.

2.2. Data availability and ethical permit

Due to Swedish regulations the data in this study cannot be shared by the authors. However, the data can be requested from the two government agencies: The National Board of Health and Welfare (socialstyrelsen@socialstyrelsen.se), and Statistics Sweden (scb@scb.se). Histopathology data can be obtained through Swedish pathology departments. The last author Dr. Ludvigsson can provide a list of the departments and their contact details. This study received approval from the Stockholm Ethics Review Board. As it was solely registry-based, there was no need for ethical approval or informed consent [19].

2.3. Definition of autoimmune disease

This study encompassed 21 autoimmune diseases associated with CeD [3, 20], defined based on the International Classification of Diseases (ICD) codes with diagnostic data from the NPR. The 21 autoimmune diseases included Addison’s disease, alopecia areata, ankylosing spondylitis, autoimmune hepatitis, autoimmune thyroiditis (Hashimoto’s thyroiditis), dermatomyositis or juvenile dermatomyositis, grave’s disease, inflammatory bowel disease, multiple sclerosis, myasthenia gravis, polymyositis, primary biliary cholangitis, psoriasis, rheumatoid arthritis, sarcoidosis, Sjogren syndrome, spondyloarthritis, systemic sclerosis, systemic/cutaneous lupus erythematosus, type 1 diabetes, and vitiligo (Table S1). In cases of multiple diagnoses, we selected the earliest recorded instance. Due to the retrospective case-control nature, we retrieved diagnoses of autoimmune diseases made before the CeD diagnosis and before the equivalent inclusion date for controls. Hence, the exposure time in this study ran up until CeD, and presumably represented time with undiagnosed CeD and ongoing gluten exposure.

2.4. Covariate assessment

Educational attainment was divided into compulsory school (0–9 years), upper secondary (10–12 years), college or university (≥13 years), and unknown (no data) with data obtained from the government agency, Statistics Sweden [21]. For every individual, we referenced the highest documented education level. For children (<16 years old), we considered the highest education attainment of their parents. The

![Fig. 1. Study population and design.](image-url)
Charlson Comorbidity Index, evaluated up to 12 months before the CeD diagnosis date/matching date, was used as an indicator of overall health status [22].

2.5. Statistical analysis

We used a histogram plot to show the age at CeD diagnosis and age at the autoimmune disease diagnosis among CeD patients and controls. We categorized individuals by CeD diagnosis age into 8 groups: 0–4, 5–9, 10–14, 15–20, 20–29, 30–39, 40–59, and ≥60 years. We then utilized conditional logistic regression to estimate the odds ratio with 95% confidence interval of autoimmune disease, comparing CeD cases with controls after the adjustment for highest educational attainment and the Charlson Comorbidity Index. In this analysis, each stratum, comprising 1 CeD case and a maximum of 5 matched controls, was independently assessed before aggregating into a summary estimate [23]. Through this method of internal stratification, influences from birth year, sex, county of residence, and calendar year on our effect measurements were mitigated. To minimize surveillance bias among individuals with a newly diagnosed autoimmune disease, who may be tested for CeD and silent CeD detected, we conducted a sensitivity analysis by removing individuals with autoimmune disease diagnosed up until 6 months before CeD diagnosis. To test sex difference, we studied women and men separately. To examine the influence of coverage alteration of NPR, we performed a sensitivity analysis stratified by calendar year (before and after 2000). In a final sensitivity analysis we included autoimmune diseases diagnosed within 6 months after CeD diagnosis to account for delayed non-celiac autoimmune diagnosis at time of CeD workup. The P values were estimated by the Wald test. All tests were two-sided and performed using R software (version 4.1.1).

3. Results

This retrospective matched case-control analysis included 46,575 CeD cases and 225,295 controls. As illustrated in Fig. 2, the diagnosis of CeD peaked at age 2 and subsequently declined as age progresses. While the onset of autoimmune diseases among CeD patients was most prevalent during childhood and young adulthood, it is notable that this peak was more pronounced during young adulthood among the control group.

As expected, CeD patients exhibited a higher prevalence of autoimmune diseases compared to their controls, as shown in Table 1. A total of 3059 (6.6%) CeD patients and 4076 (1.8%) controls had earlier autoimmune disease. Overall, the OR for autoimmune disease in CeD was 3.50 (95% CI 3.32–3.70). However, the risk of autoimmune disease did not escalate with increasing age at the CeD diagnosis (Fig. 3). Compared with controls, the odds ratio of autoimmune disease in CeD patients was 7.70 (95% CI 4.71–12.57) in those diagnosed with CeD in 0–4 years, 19.02 (95% CI 13.80–26.23) in 5–9 years, 6.18 (95% CI 5.14–7.44) in 10–14 years, 4.80 (95% CI 3.97–5.79) in 15–19 years, 4.24 (95% CI 3.55–5.07) in 20–29 years, 4.65 (95% CI 3.93–5.51) in 30–39 years, 3.67 (95% CI 3.30–4.09) in 40–59 years, and 1.67 (95% CI 1.50–1.85) in ≥60 years. The association between CeD diagnosis and autoimmune disease risk across age strata remained overall consistent in the sensitivity analysis where the individuals with autoimmune disease diagnosed in the last 6 months before CeD diagnosis had been removed (Table S2) and in the sensitivity analysis where autoimmune diseases diagnosed within 6 months after CeD diagnosis were included (Table S3). The association pattern was consistent in the analysis including men and women separately (Fig. 3) and individuals diagnosed with CeD before and after 2000 (Table S4).

Fig. 2. Distribution of age at celiac disease (CeD) diagnosis and age at autoimmune disease diagnosis in CeD cases and controls.
4. Discussion

Although CeD is increasingly common in many parts of the world, diagnosis rates remain low, and diagnosis is often delayed. While delayed diagnosis of CeD can result in prolonged patient symptoms and burden related to misdiagnosis, the impact of CeD diagnostic delay on the risk of development of secondary autoimmune disorders is uncertain. This nationwide case-control study revealed an increased risk of autoimmune disease among CeD patients compared to controls. However, the risk of autoimmune disease did not increase with the advancing age at the diagnosis of CeD, which implies that a delayed diagnosis among CeD patients, and prolonged active celiac disease or exposure to gluten in undiagnosed CeD, may not increase the risk of developing autoimmune disease.

The association between age at CeD diagnosis and the risk of autoimmune disease has been debated for many years and remains uncertain to this day. An early study including 909 CeD patients and 1268 healthy controls found that an older diagnosis age of CeD was significantly associated with higher odds of developing an autoimmune disorder. The prevalence of autoimmune disease was approximately 6 times higher among individuals with a diagnosis aged >20 years (34.0 %) compared to those aged <2 years (5.1 %) [7]. Another study including 422 CeD patients and 605 controls revealed a positive association between age at diagnosis of CeD and the odds of autoimmune disease; however, the analysis did not observe an association between actual duration of exposure to gluten and the risk of autoimmune disease [11]. In the

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CeD cases</th>
<th>Controls</th>
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<tbody>
<tr>
<td>N</td>
<td>46,575</td>
<td>225,295</td>
</tr>
<tr>
<td>Male, N (%)</td>
<td>17,550 (37.7)</td>
<td>85,027 (37.7)</td>
</tr>
<tr>
<td>Female, N (%)</td>
<td>29,025 (62.3)</td>
<td>140,268 (62.3)</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>29 (8-54)</td>
<td>29 (8-54)</td>
</tr>
<tr>
<td>Education, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compulsory school</td>
<td>10,082 (21.6)</td>
<td>49,919 (22.2)</td>
</tr>
<tr>
<td>Upper secondary</td>
<td>17,458 (37.5)</td>
<td>84,439 (37.5)</td>
</tr>
<tr>
<td>College or university</td>
<td>13,670 (29.4)</td>
<td>64,704 (28.7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>5365 (11.5)</td>
<td>26,233 (11.6)</td>
</tr>
<tr>
<td>Charlson comorbidity index, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>36,522 (78.4)</td>
<td>195,767 (86.9)</td>
</tr>
<tr>
<td>1</td>
<td>4925 (10.6)</td>
<td>14,179 (6.3)</td>
</tr>
<tr>
<td>2</td>
<td>1986 (4.3)</td>
<td>7402 (3.3)</td>
</tr>
<tr>
<td>3+</td>
<td>3138 (6.7)</td>
<td>7912 (3.5)</td>
</tr>
<tr>
<td>Autoimmune disease, N (%)</td>
<td></td>
<td></td>
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<tr>
<td>All age strata</td>
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<tr>
<td>0-4</td>
<td>3059 (6.6)</td>
<td>4076 (1.8)</td>
</tr>
<tr>
<td>5-9</td>
<td>140 (0.3)</td>
<td>135 (0.1)</td>
</tr>
<tr>
<td>10-14</td>
<td>319 (0.7)</td>
<td>157 (0.1)</td>
</tr>
<tr>
<td>15-19</td>
<td>329 (0.7)</td>
<td>282 (0.1)</td>
</tr>
<tr>
<td>20-29</td>
<td>251 (0.5)</td>
<td>266 (0.1)</td>
</tr>
<tr>
<td>30-39</td>
<td>277 (0.6)</td>
<td>299 (0.1)</td>
</tr>
<tr>
<td>40-59</td>
<td>327 (0.7)</td>
<td>323 (0.1)</td>
</tr>
<tr>
<td>60+</td>
<td>776 (1.7)</td>
<td>924 (0.4)</td>
</tr>
<tr>
<td>60+</td>
<td>640 (1.4)</td>
<td>1690 (0.8)</td>
</tr>
</tbody>
</table>

IQR, interquartile range.

Fig. 3. Odds ratio (OR) with 95 % confidence interval (CI) of autoimmune disease comparing celiac disease cases to controls by age at CeD diagnosis in the retrospective matched case-control analysis.
Several potential mechanisms may explain our null association between advanced CeD diagnosis age (likely longer gluten exposure and duration of active CeD whilst undiagnosed with CeD), and higher autoimmune disease risk. While the most likely explanation is that longer duration of undiagnosed CeD does not cause other autoimmune disease, we cannot rule out other explanations for our findings. Firstly, a substantially heightened risk of autoimmune disease for early diagnosed CeD (where we assume a short exposure to undiagnosed CeD) may be attributed to a more severe nature, such as more serious symptoms and excessive mortality in childhood CeD, thereby hiding an detrimental effect of long duration of undiagnosed CeD. Secondly, the much higher odds ratio in childhood and young adulthood might be due to the lower prevalence of autoimmune disease in controls of that age. Thirdly, a stronger association with autoimmune disease for early CeD in childhood or young adulthood may be influenced by the overall young onset age of most autoimmune diseases. Our data observed that the onset of autoimmune disease was more prevalent during childhood and early adulthood among both CeD patients and controls, which partly support this hypothesis. Fourthly, testing for CeD has increased over time. Testing for CeD is recommended at the diagnosis of several autoimmune diseases, and it cannot be ruled out that the pool of undiagnosed CeD is low among patients with autoimmune disease later in life. While autoimmunity may increase over age, autoimmune disease may not continue to rise and that with testing for CeD in earlier age, may also contribute to the lower prevalence of autoimmune disease in people diagnosed with CeD at 60 years or later. Fifthly, some calendar effects cannot be ruled out. As we have demonstrated for CeD, the incidence of certain autoimmune diseases has changed over time. Finally, the structure of the Swedish NPR may have influenced our findings (after 2001, the year NPR included data from outpatient, all autoimmune diagnoses increased in prevalence since many of them do not require inpatient care). Even if we adjusted for calendar year and observed a consistent result in the analysis stratified on calendar year 2001, this may still have impacted on our findings and could have contributed to the flat prevalence of autoimmunity between ages 10 and 40 in our study.

But despite all arguments to the contrary, we note that our findings did not support a higher risk of autoimmune disease in old age and potentially caused by a delayed CeD diagnosis. The main implications of this study are hence outside the need for early diagnosis to prevent later autoimmune comorbidity. An increased risk of autoimmune disease in CeD patients was still detected across all age strata, which informs that autoimmune disease screening and early detection should not be neglected at any life stage, but not particularly so in the elderly. A significantly high risk of autoimmune disease was found among the early-onset CeD, which requires that clinicians, in particular, pediatricians pay more attention to autoimmune disease among this population.

The strengths of this study include a large number of CeD patients, accurate diagnosis of a comprehensive list of autoimmune diseases, and limited selection bias due to the nationwide coverage. A sensitivity analysis excluding patients with autoimmune disease diagnosed 6 months up to CeD diagnosis to decrease surveillance bias confirmed our main findings. The study has some limitations that need to be acknowledged. First, we lack data on obesity and lifestyle factors, such as smoking, which may introduce residual confounding even though obesity and smoking may not be associated with CeD risk. Second, we have no data on adherence to a gluten-free diet or CeD activity, which means that the advanced age at the CeD diagnoses is not necessarily identical to prolonged gluten exposure, even though the gluten-free diet is not that prevalent among the general population.

In summary, this nationwide matched case-control study did not support an increased risk of autoimmune disease due to an advanced diagnosis age of CeD and presumably longer duration of gluten exposure in undiagnosed CeD. Instead, a higher risk of autoimmune disease was detected among the CeD diagnosed in early childhood which suggested the necessity of a high autoimmune disease awareness in this population.

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CRediT authorship contribution statement

Shuai Yuan: Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing.

Daniel Leffler: Conceptualization, Investigation, Methodology, Validation, Writing – review & editing.

Benjamin Lebwohl: Conceptualization, Investigation, Methodology, Validation, Writing – review & editing.

Peter H.R. Green: Conceptualization, Investigation, Methodology, Validation, Writing – review & editing.

Jonas Söderling: Data curation, Investigation, Methodology, Resources, Validation, Writing – review & editing.

Jiangwei Sun: Investigation, Methodology, Project administration, Validation, Writing – review & editing.

Jonas F. Ludvigsson: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

Dr. Leffler is an employee of Takeda.

Dr. Ludvigsson has coordinated an unrelated study for the Swedish IBD quality register (SWIBREG). That study received funding from Janssen Corporation. Dr. Ludvigsson has also received financial support from MSD, developing a paper reviewing national healthcare registers in China. Dr. Ludvigsson has an ongoing research collaboration with Takeda.

The other authors report no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaut.2024.103170.

References


