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Meta-analysis

High Prevalence of Celiac Disease in Autoimmune Hepatitis: A Systematic Review and Meta-analysis

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ABSTRACT

Background: Recent studies investigating the prevalence of celiac disease (CD) in patients with autoimmune hepatitis (AIH) have revealed highly variable findings. We therefore aimed to evaluate the prevalence of CD in cases with AIH.

Methods: Two independent professional librarians searched Scopus, EBSCO, Google Scholar, PubMed, EMBASE, Cochrane and Web of Science Core Collection from inception to November 2021. The terms used in our systematic search included 'celiac disease', 'celiac', 'transglutaminases', 'gluten', 'gliadin', 'EMA', 'TTG' and 'villous' in combination with 'autoimmune', 'hepatitis', 'ANA', 'SMA' and 'LKM'. This investigation yielded 645 unique published papers. A systematic review based on the PRISMA guidelines resulted in 56 papers eligible for full text evaluation. Fifteen papers were deemed eligible, with 8 being included in our main pooled analysis.

Results: Our main analysis included 567 cases with AIH from eight papers, where biopsy-verified CD (equivalent to Marsh III) was reported in 23 subjects (4.1%). The pooled prevalence of CD in AIH was 4.5% (95% CI = 3%-6.8%) (heterogeneity: P = 0.52; I2 = 0), which is considerably higher than the 1% CD reported in most general populations. When also including papers where CD had been diagnosed through positive serology without biopsy (15 studies: n = 1817 cases with AIH), the pooled prevalence of CD was 5.4% (95% CI = 3%-9.5%) (heterogeneity: P < 0.01; I2 = 84.49%).

Conclusion: Our findings showed a higher prevalence of CD in cases with AIH compared to the healthy subjects. CD screening should be carried out in cases with AIH.

Keywords: Autoimmune hepatitis, celiac disease, meta-analysis, prevalence.

Introduction

Autoimmune hepatitis (AIH) is a severe chronic and progressive autoimmune liver disease known by immune-mediated inflammatory process in the liver that may lead to cirrhosis and liver failure (1, 2). Previous studies reported the incidence of AIH between 0.85 and 1.68 per 100 000 person-years, predominantly afflicting females. AIH may have a multifactorial etiology, where both genetics, immune response regulation and environmental factors have a pivotal role (2). AIH have been associated with several extrahepatic autoimmune

diseases, including autoimmune thyroiditis, diabetes, rheumatoid arthritis, inflammatory bowel disease and potentially also to celiac disease (CD) (3, 4). CD is an immune-mediated enteropathy initiated by gluten in genetically susceptible subjects and is known by circulating celiac-specific autoantibodies and gastrointestinal manifestations including malabsorption resulted from by small intestinal villous atrophy but also extraintestinal manifestations. In prior investigations, the rate of CD has ranged from 2% to 20% in children and adults with AIH (4, 5). While the rate of CD in AIH cases is thought to be higher than in the general population (~1%), prior investigations have been small, mostly single-center investigations leading to large variability in findings and lack of exact estimates. It is well established that CD is associated with different types of liver diseases and that the application of a gluten-free diet has been proposed to improve liver damages in CD-associated hepatopathy, autoimmune cholangitis and non-alcoholic fatty liver disease (NAFLD) (6-8). Although the findings are more sparse in those who have AIH, there is one study that indicated that, in cases with AIH, the application of a gluten-free diet for CD improved liver injury, whereas the AIH management alone had not been satisfying in liver recovery. However, it remains unclear whether CD worsens AIH severity or causes separate liver damages in addition to AIH (6, 7). Because of the highly varying CD prevalence results in AIH in earlier reports, we aimed to conduct a meta-analysis based on currently available findings to investigate the prevalence of CD in AIH.

Methods

Search Strategy

Two independent professional librarians performed a systematic search of Scopus, EBSCO, Google Scholar, PubMed (Medline), Cochrane, EMBASE and Web of Science Core Collection from inception to November 2021 The terms used in our systematic search included ‘celiac disease’, ‘celiac’, ‘coeliac’, ‘transglutaminases’, ‘gluten’, ‘gliadin’, ‘EMA’, ‘TTG’, ‘villus’, ‘villous’ in combination with ‘autoimmune’, ‘hepatitis’, ‘liver’, ‘ANA’, ‘SMA’ and ‘LKM’. The authors reviewed all the search process. In order to increase quality of systematic search, a broad search strategy was used, yielding a total of 1456 papers (after removal of duplicates, 645 unique papers remained).

Finally, 56 papers were deemed eligible for full-text review.

Eligibility Criteria

After full-text evaluation, papers with non-English language, poster presentations, conference abstracts, letters to editors, review articles, meta-analyses and papers without appropriate results were excluded (Figure 1). For our main statistical analysis, CD had to be biopsy-proven with villous atrophy. In a complementary analysis, a broader definition of CD was considered, also including papers where CD was approved with at least one positive serological marker (tissue transglutaminase antibody (TTG), endomysial antibody (EMA) or antigliadin antibody (AGA)). The complementary analysis included a total of 15 papers.

Data Collection

The PRISMA guidelines were followed, and eligible papers were assessed in detail two independent authors. From each paper, publication date, country of origin, age of the cases, CD definition and AIH definition, number of cases with AIH, number of AIH cases with CD, number of healthy controls, number of controls with CD, number of cases with a positive serology, number of cases with a biopsy-proven CD, Marsh grade (III) for the definition of CD and study design, were extracted.

Statistics

Statistical analysis was performed using Comprehensive Meta-analysis (CMA) Software version 3. The prevalence was reported with 95% confidence intervals. The heterogeneity was considered as I2 higher than 50% or a P-value < 0.05. Publication bias was evaluated using Egger’s test and Funnel plot. The prevalence of CD in AIH was calculated using random and fixed models.

Results

After review of abstracts and titles, 56 articles were thought to be eligible for full-text evaluation. Out of these, 15 articles were deemed relevant, and 8 of these had needed biopsy with villous atrophy (Marsh III) for the celiac diagnosis, thus included in the main pooled analysis. The reasons for excluding 41 articles were: data only from correspondence/letter to editor (n = 4), congress abstract (n = 6), poster presentation (n = 3), review article (n = 5), meta-analysis (n = 1), insufficient/incorrect data (n = 16)

and non-English article (n = 6). The selection process is described in Figure 1.

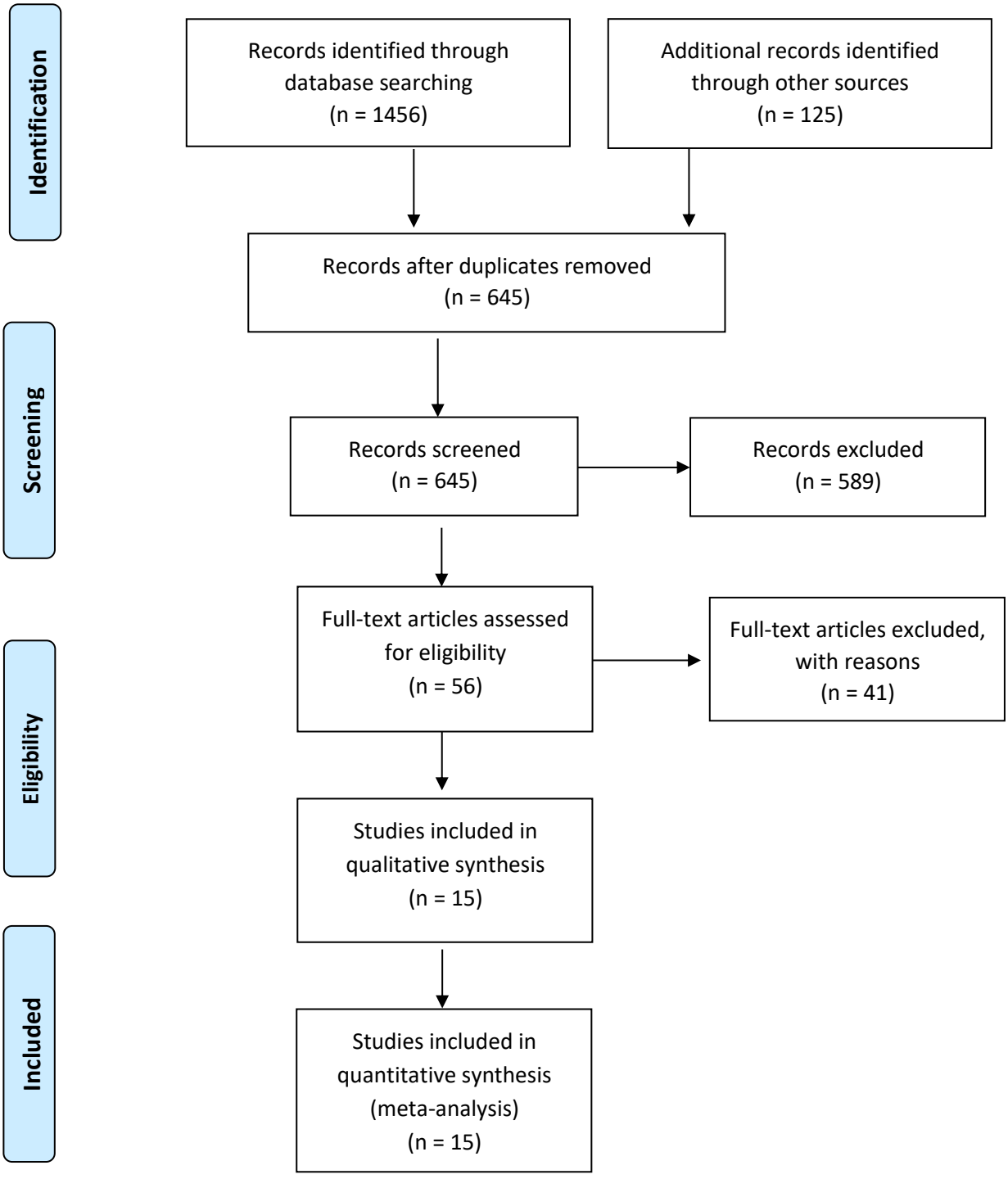

Figure 1. PRISMA flowchart of the literature search and selection of studies that reported prevalence of celiac disease in autoimmune hepatitis.

Study Characteristics

For our meta-analysis, 15 articles were deemed relevant, where 8 reported biopsy-proven (with positive serology screening first) CD as the primary outcome and 7 also included serology-proven (Table 1). About half of the papers had a prospective study design (n = 7), 4 were retrospective, and the

remaining articles were a combination of retro- and prospective, except 1 paper which had both prospective and cross-sectional designs. Five papers included their cases consecutively and 6 papers had control groups. Sixty percent of the published papers originated from Europe. In most articles, women made up at least 65% of the study cases (3 papers reported no information on the proportion of females and in 1 paper, women made up 46%, Table 1). To be eligible for our main analysis (n = 8), we needed that the investigators reported that Marsh III (villous atrophy) was required for the approval of CD diagnosis. AIH was diagnosed in the majority of studies using either the original 1993 score, revised 1999 score or the 2008 simplified score created by the International Autoimmune Hepatitis Group, all of which are appropriate criteria to detect AIH by societal recommendations. Missoum et al. (9) used serologic markers, but did not provide more diagnosis data. Rubio-Tapia et al. (10) diagnosed AIH in liver transplant recipients using chart review, in which, in the US, explant pathology information is available for approving diagnosis and the United Organ Sharing Network (UNOS) tracks liver transplant diagnoses. While Sjoberg et al. (11) did not use a particular score system, they used liver biopsy and serology to diagnose AIH, which is also approved per society recommendations.

Eighty-seven percent of the papers did not monitor for CD at the time of AIH diagnosis. Participant age varied between the papers, where 9 had a combination of children and adults, 2 consisted exclusively of children and 4 consisted of adults Only 3 papers stated specifically that they followed-up their cases.

Table 1. Characteristic of the included studies.

Authors	Year of Publication	Number of patients with AIH	Number of Patients with CD	Prevalence of CD (%)	Biopsy for Diagnosis of CD
Sjoberg et al. (11)	1997	37	2	5.4	Yes
Volta et al. (13)	1998	181	5	2.8	Yes
Germenis et al. (17)	2005	38	0	0	No
Villata et al. (18)	2005	47	3	6.4	Yes
Rubio-Tabia et al. (10)	2008	43	15	34.9	No
Mirzaagha et al. (19)	2010	51	1	2	Yes
Sima et al. (20)	2010	84	2	2.4	Yes
Teufel et al. (21)	2010	278	3	1.1	No
El-Shabrawi et al. (12)	2011	26	3	11.5	Yes
Drastich et al. (22)	2012	77	4	5.2	Yes
Nastasio et al. (14)	2013	79	15	19	No
Najafi et al. (23)	2014	64	3	4.7	Yes
Van Gerven et al. (24)	2014	460	16	3.5	No
Muratori et al. (25)	2015	327	12	3.7	No
Missoum et al. (9)	2019	25	2	8	No

AIH: Autoimmune hepatitis; CD: Celiac disease.

Prevalence of Biopsy-Verified CD in AIH

The 8 identified papers for our main analysis contained 567 cases with AIH. Of these, 23 (4.1%) had a diagnosis of CD. After waiting for study size and using a fixed-effect model, we found a pooled prevalence of CD of 4.5% (95% CI = 3%-6.8%)

(Figure 2), with a low heterogeneity of 0.0% (P=0.52). Restricting data to papers where ≥75% of AIH cases were women, we showed a CD prevalence of 2.9%. Due to the low heterogeneity in our main analyses, no other subgroup analyses were performed.

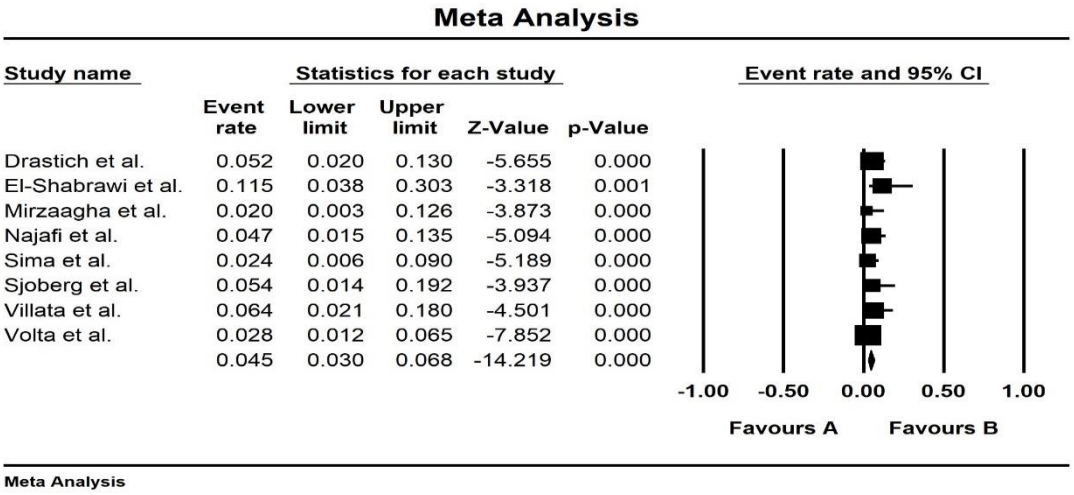

Figure 2. Prevalence of CD in patients with AIH based on the results of biopsy.

Prevalence of CD, Defined Through Biopsy or Positive Serology, in AIH

When allowing subjects of CD defined either through biopsy (Marsh III) or celiac serology (TTG, EMA or AGA immunoglobulin A/immunoglobulin G), we found 15 papers with 1817 cases (Figure 3). The pooled prevalence of CD according to this definition was 5.4% (95% CI = 3%-9.5%) (heterogeneity: P<0.01; I2 = 84.49%). Restricting the analyses to 2005 and later, when serology was unlikely to find AGA, did not change the pooled prevalence of CD.

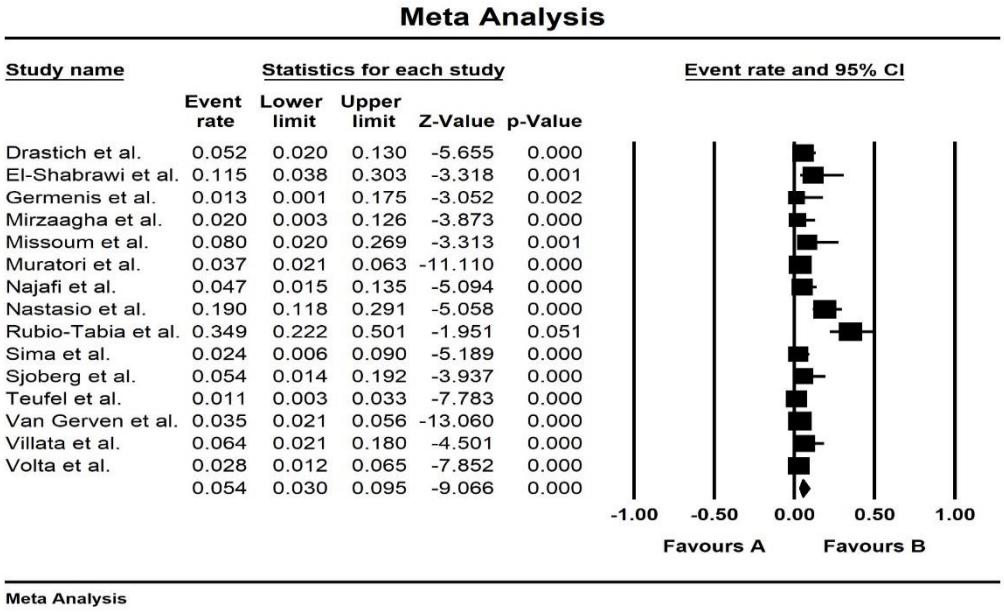

Figure3. Prevalence of CD in patients with AIH based on the results of biopsy or positive serology.

Risk of Bias Across Studies

A funnel plot revealed signs of publication bias, in that smaller papers were more likely to be published if they found higher prevalence of CD in AIH than if they reported a lower prevalence. Egger's test P-value=0.29. Furthermore, the funnel plot shows no publication bias (Figure 4).

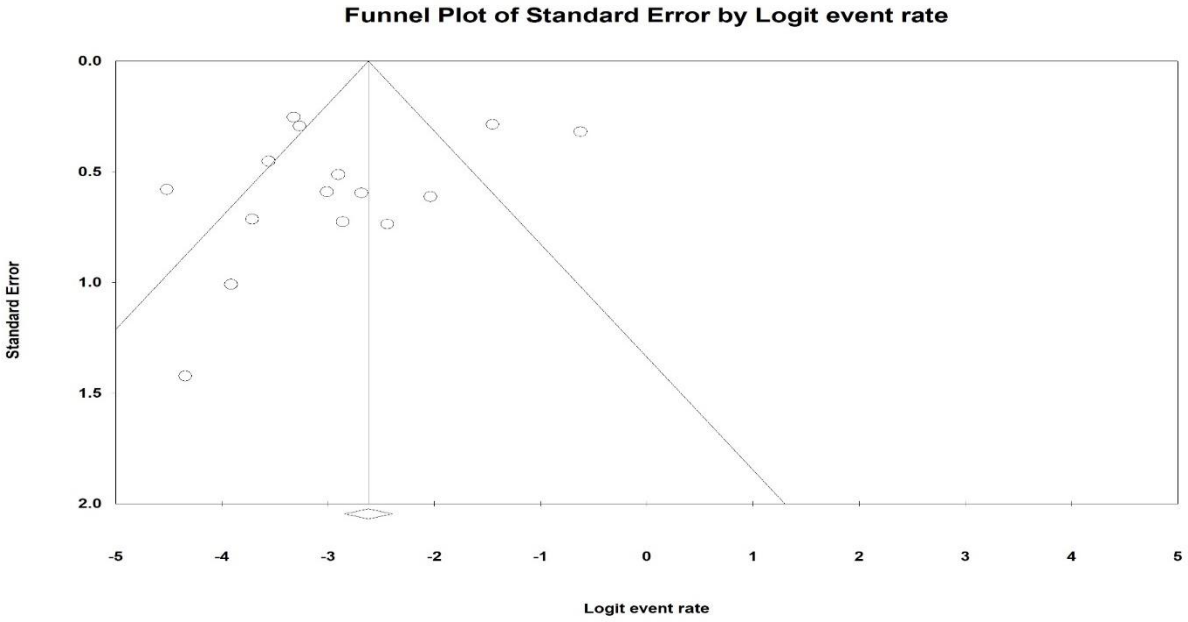

Figure 4. Funnel plot of the included studies for evaluation of publication bias.

Meta-Regression

We used meta-regression to evaluate possible correlations between prevalence of CD and publication year and sample size of the studies. As shown in the Figure 5, as the publication year of the studies increased, the prevalence of CD increased (P = 0.71). Based on the Figure 6, the prevalence of CD decreased with increasing sample size (P = 0.10).

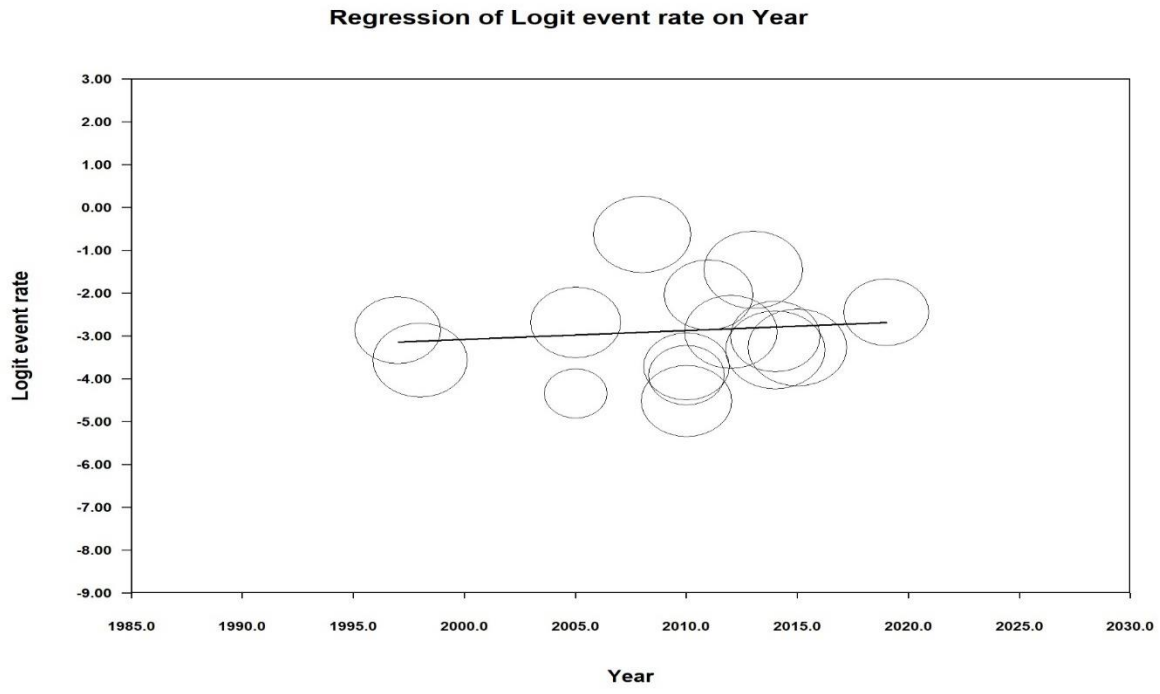

Figure 5. Meta-regression plot of the correlation between the prevalence of CD and the year of included studies.

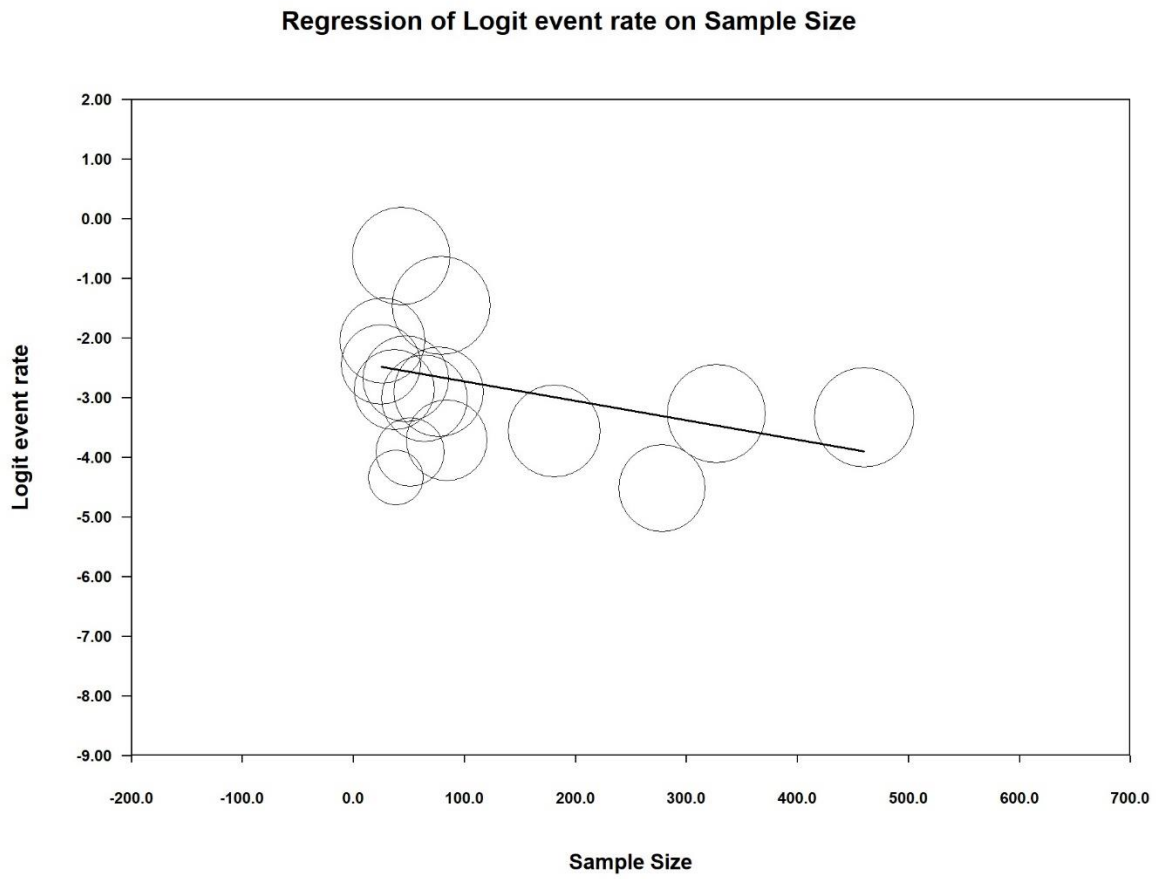

Figure 6. Meta-regression plot of the correlation between the prevalence of CD and the year of included studies.

Discussion

Our meta-analysis showed that the pooled prevalence of biopsy approved CD in cases with AIH was 4.5% and 5.4% if combining both biopsy- or serology verified CD. Our main analysis with biopsy-proven CD consisted of 8 papers comprising 567 cases, and our second analysis with combined biopsy- or serology proven CD consisted of a total of 15 papers comprising 1817 cases, including both children and adults. While we are aware of one earlier meta-analysis on CD in cases with AIH, that meta-analysis only assessed children (age 0-18 years), was limited by a smaller number of cases with AIH (n = 206) and mixed biopsy- and serology-proven CD. Moreover, it was based on only 3 studies, 2 of which we excluded as these did not have our inclusion criteria. The shared publication included in both meta-analyses was the paper by El-Shabrawi et al. (12) The 3.5% pooled prevalence of biopsy-proven CD in cases with AIH was considerably higher than the overall prevalence of around 1% of CD found in most general populations. AIH and CD may have some similarities with respect to gene coding for class II human leukocyte antigens, which may clarify their concurrent existence. Volta et al. (13)have reported that the presence of CD in AIH cases was mostly asymptomatic, where only the cases off AIH therapy had bowel manifestations, which could propose that the immunosuppressive treatment may disguise CD manifestations and thereby delay essential diagnosis. Nastasio et al. (14) showed a significantly higher rate of sustained remission in medication-free AIH cases who adhered to a gluten-free diet compared to cases with AIH but no CD. Another paper has also proposed that gluten removal may considerably improve liver damage, where AIH treatment alone had not given satisfying outcomes (15). This effect could be due to an enhanced intestinal permeability with both circulating and residual tissue transglutaminase antibodies in the liver, modifying self-antigens causing liver damage. Current recommendations about AIH from the American Association for the Study of Liver Diseases suggest monitoring AIH cases for CD at diagnosis. Ours is the largest meta-analysis that includes both children and adults, and the data support the statement of celiac monitoring in the AIH protocols and additionally provide a more

accurate estimate of the prevalence of CD in AIH. However, the protocols do not state specifically how the monitoring for CD should be carried out. An initial serology-based CD monitoring could possibly be applied as opposed to esophagogastroduodenoscopy with biopsy given that the prevalence of CD using both definitions is very similar with overlapping CIs 4.5% (95% CI = 3%-6.8%) vs combining biopsy and serology: 5.4% (95% CI = 3%-9.5%). This would most likely be a more cost-effective and less invasive technique for CD monitoring. CD monitoring may also possibly be carried out more than once, not only at AIH diagnosis, as concurrent autoimmune diseases, including CD, could develop over time. This high rate of CD diagnosis found in our findings could be an underestimate of the rate of CD in AIH. This is due to the treatment of AIH (steroids, prednisone, budesonide and immunosuppressants) is very effective at treating cases with CD, resolving manifestations, impacting on serological evaluations and improving/resolving biopsies. If evaluating for CD had been made at diagnosis of AIH in all investigations, we would have a better knowledge of CD prevalence. However, the majority of the included studies did not assess for CD at AIH diagnosis and were in the majority of subjects conducted before the new protocols suggesting CD monitoring at AIH diagnosis were reported. Performing serological monitoring for CD after initiation of AIH treatment may falsely lower the diagnostic rate of CD. Ideally, CD evaluation should be suggested at AIH diagnosis as well as later, if any digestive manifestations or other signs or symptoms of CD are present, similar to current suggestions for type 1 diabetes cases. It was beyond the scope of this paper to evaluate suitable monitoring intervals, but we encourage future investigations to assess this topic to benefit cases with AIH.

Strengths and Limitations

A broad search strategy was applied to improve the sensitivity of our study, yielding a total of 1456 papers, where 31 papers were deemed relevant for full-text review and 15 were included in our meta-analysis. To the best of our knowledge, this is the only truly large-scale meta-analysis (567 subjects in our main analysis and 1817 subjects with AIH in our secondary analysis), evaluating the prevalence of CD in AIH, including both children and adults. The large sample size provided the condition to calculate exact prevalence estimates with narrow CIs. We applied two different definitions of CD, one to increase specificity (biopsy only) and another one to reflect the increased application of serology to diagnose CD. Using two definitions of CD were valuable in determining whether a more cost-effective and less-invasive monitoring for CD using serologies could possibly be applied in AIH cases as opposed to esophagogastroduodenoscopy. This investigation has also some limitations. The diagnostic criteria for AIH have modified over time. However, all the included investigations were published in 1996 or later, when viral hepatitis (including hepatitis C virus diagnosed in 1990) could be ruled out, and the scoring systems for AIH diagnosis had been formed (although the main revised criteria were made in 1999). Furthermore, the diagnostic criteria for CD have modified throughout the years. Interestingly, the pooled rate of biopsy-verified CD was higher in our investigation than that of serology- or biopsy-verified CD diagnosis, 5.4% (95% CI = 3%-9.5%) vs 4.5% (95% CI = 3%-6.8%), although the latter is a more liberal set of criteria. Since serology based CD tends to be more common than biopsy-verified CD (however often preceded by a positive serology), our findings do not show that serology-positive CD is less prevalent, only that investigations based on serological markers found on average lower CD prevalence. Interestingly, the 95% CI for the two outcomes were overlapping. We included AGA in our search terms for serology-based CD since that antibody was applied in older investigations of CD; however, AGA may overestimate the rate of CD due to false-positive cases. Moreover, we cannot rule out that publication bias has affected our findings since smaller investigations may have been published more often if they revealed a higher rate of CD. Taken together, our investigation had limited power in sub-analyses, and we were unable to estimate, for instance, area-specific prevalence of CD. In a meta-analysis by Singh et al. (16) the prevalence of CD varied between 0.4% in South America and 0.8% in Europe and Oceania (general population), and we cannot rule out that CD is both more and less common in AIH populations in different parts of the world.

Conclusion

The meta-analysis showed a high prevalence of CD in cases with AIH. Taken together, our analysis proposed that cases with AIH may benefit from CD screening.

Declarations

Acknowledgement

The author thanks all those who contributed to this study.

Author Contribution

Antoni Riera-Mestre: Study design, data collection, writing draft of study.

Juan Torres-Macho: Study design, data collection, writing draft of study

Cristina Carretero: Study design, data collection, writing draft of study

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Conflict of interest

There is no conflict of interest.

Data Availability

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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