

Increased risk of non-alcoholic fatty liver disease after diagnosis of celiac disease

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Background & Aims: Non-alcoholic fatty liver disease is a common cause of chronic liver disease. Celiac disease alters intestinal permeability and treatment with a gluten-free diet often causes weight gain, but so far there are few reports of non-alcoholic fatty liver disease in patients with celiac disease.

Methods: Population-based cohort study. We compared the risk of non-alcoholic fatty liver disease diagnosed from 1997 to 2009 in individuals with celiac disease ($n = 26,816$) to matched reference individuals ($n = 130,051$). Patients with any liver disease prior to celiac disease were excluded, as were individuals with a lifetime diagnosis of alcohol-related disorder to minimize misclassification of non-alcoholic fatty liver disease. Cox regression estimated hazard ratios for non-alcoholic fatty liver disease were determined.

Results: During 246,559 person-years of follow-up, 53 individuals with celiac disease had a diagnosis of non-alcoholic fatty liver disease (21/100,000 person-years). In comparison, we identified 85 reference individuals diagnosed with non-alcoholic fatty liver disease during 1,488,413 person-years (6/100,000 person-years). This corresponded to a hazard ratio of 2.8 (95% CI 2.0–3.8), with the highest risk estimates seen in children (HR = 4.6; 95% CI 2.3–9.1). The risk increase in the first year after celiac disease diagnosis was 13.3 (95% CI 3.5–50.3) but remained significantly elevated even beyond 15 years after the diagnosis of celiac disease (HR = 2.5; 95% CI 1.0–5.9).

Conclusion: Individuals with celiac disease are at increased risk of non-alcoholic fatty liver disease compared to the general population. Excess risks were highest in the first year after celiac disease diagnosis, but persisted through 15 years after diagnosis with celiac disease.

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Introduction

Celiac disease (CD) is associated with both acute and chronic liver diseases, especially autoimmune liver disease [1,2]. Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in children and adolescents in Western nations [3], it is estimated to be present in 20% of the population [4], and some individuals may progress to fibrosis and cirrhosis [4,5]. Yet, data establishing whether individuals with CD may be at risk of NAFLD are nascent [1,6]. Metabolic risks as well as those altering intestinal permeability found in CD can also be potential triggers for NAFLD.

Obesity and metabolic syndromes are accepted as major accessory complications of NAFLD [7], though not all patients with NAFLD are obese [8]. A high-fat diet and sedentary lifestyle are adaptable risks, modifications to these can yield improvements in NAFLD [9], and recovery after weight loss may be related to reduced insulin resistance [10]. Many adults and children with CD are overweight or obese at diagnosis, or become overweight after treatment [11,12], consequently increasing the risk to develop NAFLD. Children [13] and adults [14] with CD may have increased cardiovascular risks which overlap with those associated with NAFLD.

The gut-liver axis via the portal system has been implicated as a potential route of inflammatory cytokines, which may trigger the onset of non-alcoholic steatohepatitis (NASH). Levels of endotoxin (lipopolysaccharide), derived from intestinal Gram-negative microbiota, are elevated in the sera of adults [15] and children [16] with NAFLD, suggesting these individuals have increased intestinal permeability. Small intestinal bacterial overgrowth (SIBO) is more common among patients with NAFLD than healthy individuals [17] and is associated with higher TNF- α levels, independent of increases in gut permeability markers [18]. Individuals with CD have altered intestinal permeability due to the disturbance of mucosal integrity induced by gluten and the associated inflammatory response [19]. Additionally,

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Abbreviations: CD, celiac disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; SIBO, small intestinal bacterial overgrowth; VA, villous atrophy; ICD, international classification of disease (codes); CI, confidence interval; HR, hazard ratio; OR, odds ratio; BMI, body mass index.



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SIBO is common among individuals with CD [20], which may further impair mucosal barriers and may have other links to the pathogenesis of NAFLD [18]. Whether a compromised intestinal barrier is a cause or effect of NAFLD requires additional study, though the prevailing theory is that bacteria-derived endotoxin and related cytokines may serve as a “second hit” among certain patients with hepatic steatosis leading to the development of NASH [21].

In this population-based study, we aim to investigate the frequency with which NAFLD is identified among individuals with CD.

Materials and methods

Study participants

In 2006–2008 we collected small intestinal biopsy record data from all 28 pathology departments in Sweden. The biopsies had been performed between 1969–2008 and collected data included date of biopsy, biopsy site (duodenum or jejunum), morphology codes consistent with villous atrophy (VA), (Marsh grade III) (see [Supplementary Table 1A](#)), and personal identity number (PIN) [22]. In this paper we equated VA with CD (details of the data collection have been published before) [23]. While we did not require positive CD serology for a CD diagnosis, patient chart validation in a random subset of individuals with VA found 88% were positive for transglutaminase, endomysium or gliadin antibodies at the time of biopsy [22].

We then matched each individual with CD with up to five reference individuals matching; age, sex, calendar year and county of residence at the time of biopsy. Reference individuals were sampled from the Swedish Total Population Registry maintained by the government agency Statistics Sweden. Through this matching procedure, for example, a woman born in 1963 with a CD diagnosis in 1998 living in the county Dalarna was matched to up to five other women, born in 1963, living in that county in 1998. After removal of duplicates and potential data irregularities, our remaining study participants (29,096 CD patients and 144,522 reference individuals) were identical to that of our mortality study in CD [24].

NAFLD, other liver disease, and alcohol use

Patients with our outcome measure, NAFLD, were identified using a search for the ICD-10 (International Classification of Disease) code K76.0 in the Swedish Patient Registry, a registry of patient diagnoses initiated in 1964 which became nationwide in 1987. More than 99% of all somatic care is registered in the registry and most disorders have a positive predictive value of 85–95% [25]. Prior to the year 2000, the patient registry only contained inpatient data, but since 2000 has included both inpatient and hospital-based outpatient data. We restricted our follow-up to 1997–2009 since the Swedish ICD-10 began in 1997 (before that, NAFLD could not be distinguished from other liver disease).

Initially, to rule out that CD had been diagnosed due to prior liver disease (e.g. misclassified NAFLD), we excluded individuals with any liver disorder diagnosed before a first intestinal biopsy with VA ($n = 948$; 3.3%) or before the corresponding date in reference individuals ($n = 3217$; 2.2%). Hence, all study participants were free of a diagnosis of liver disease at study entry.

Since alcohol is a predominant cause of fatty liver disease, we also identified all individuals with a lifetime diagnosis of alcohol-related disease (see [Supplementary Table 2](#) for relevant ICD codes) (CD: $n = 812$, 2.8%; and reference individuals: $n = 3845$; 2.7%). These ICD codes represent both somatic and psychiatric disorders where alcohol use has been implicated and did, in some circumstances, overlap with individuals who had a prior diagnosis of liver disease. Swedish National Registries do not otherwise record alcohol use in healthy people. At this stage we also excluded study participants with a follow-up that ended before 1997 (CD: $n = 723$ (2.5%); reference: $n = 2899$ (2.1%)) since they could not potentially be diagnosed with fatty liver since that diagnosis was only introduced in 1997.

Finally, our analyses were carried out stratum-wise. We compared each CD individual only with his/her matched reference individuals and thereafter calculated a summary estimate for NAFLD, excluding reference individuals in strata

where the CD individual had been excluded for any reason. The final dataset therefore consisted of 26,816 individuals with CD and 130,051 reference individuals ([Table 1](#)).

Main covariates

The government agency Statistics Sweden delivered data on the following potential confounders: country of birth (Nordic vs. not Nordic), educational level, and socioeconomic status at the time of biopsy. When a child did not have data on socioeconomic status or education, parental data were used. Crude and adjusted risk estimates were limited to individuals with complete data on socioeconomic status and education (72.0% of CD patients and 72.5% of reference individuals had complete data on these covariates). We categorized education into four groups (≤ 9 years of primary school, 2 years of high school, 3–4 years of high school, college/university) while socioeconomic status was categorized into six groups (in accordance with the European Socioeconomic Classification, ESeC: levels 1, 2, 3+6, 7, 8, and 9). (For additional details see our previous paper [26]).

Statistics

Hazard ratios (HRs) for NAFLD were estimated using internally stratified Cox regression, with all comparisons made within a stratum of matched individuals as in a conditional logistic regression. The proportional hazards assumption was tested using log-minus-log curves ([Supplementary Fig. 1](#)). Although we found that the assumption of proportional hazards was not violated, we calculated follow-up specific HRs since the HR for NAFLD was substantially higher in the first year after CD diagnosis. We began follow-up on the date of first biopsy with VA (equivalent to CD in our study) and on the corresponding date in matched reference individuals or on Jan 1, 1997, whichever occurred latest. Follow-up time ended with NAFLD diagnosis, December 31, 2009, emigration, or death, whichever occurred first.

In pre-defined analyses, we calculated HRs for NAFLD in males-females, different age strata (e.g. ≤ 19 years, see also [Table 1](#)), and calendar year ([Table 1](#)). Potential effect modification was tested by entering interaction terms in the statistical models. We also carried out separate analyses adjusting for country of birth, level of education, and socioeconomic status.

In a post hoc analysis, we also examined the risk of NAFLD in 11,121 CD patients with Marsh 1–2 lesions (inflammation but no VA). The data collection of these individuals has been described before [27] and was identical to that of CD, except that other SnoMed codes were used (see [Supplementary material](#)).

In a sensitivity analysis we tested if the association between CD and NAFLD changed using attained age instead of time since biopsy as the time scale. Finally, we examined if adjustment for a type 2 diabetes, autoimmune thyroid disease, lipid-lowering drugs (as proxy for dyslipidemia) or drugs linked to NAFLD would influence the association between CD and NAFLD. Drug treatment was identified using relevant ATC codes in the Swedish Prescribed Drug Registry ([Supplementary material](#)). Type 2 diabetes and autoimmune thyroid disease were identified according to relevant ICD codes in the Swedish Patient Registry ([Supplementary material](#)). This latter registry started on July 1, 2005 and hence we restricted this last analysis to individuals who had not died or emigrated prior to this date.

Prior NAFLD and later CD

To investigate if a positive association with NAFLD was present before CD diagnosis, we performed a case-control study of 16,865 individuals with CD diagnosed in 1997 or later, and 83,767 matched controls. Data were analyzed using a conditional logistic regression model which eliminated the influence of the matching criteria (age, sex, birth year, and county). In *a priori* analyses we stratified for time between NAFLD and later CD (< 1 year, 1–5 years, and > 6 years).

Statistical analyses were performed using SPSS 22 (SPSS Statistics, Version 22.0, Armonk, NY). p values < 0.05 were considered to be statistically significant.

Ethics

This study was approved by the Regional Ethical Review Board in Stockholm (2006/633-31/4). Because this was a registry-based study, no participant was contacted and all data were anonymized prior to data analyses.

Table 1. Characteristics of Study Participants.

	Matched reference individuals	Celiac disease
Total	130,051	26,816
Age at study entry (yr), N (%)		
0-19	57,029 (43.9)	11,488 (42.8)
20-39	24,478 (18.8)	5044 (18.7)
40-59	27,984 (21.5)	5815 (21.7)
60	20,560 (15.8)	4509 (16.8)
Entry year (median, range)	1999, 1969-2008	1999, 1969-2008
Follow-up, years (median, range)	10, 0-41	10, 0-40
Follow-up, years (mean $\pm$ SD)	11.4 $\pm$ 6.4	11.4 $\pm$ 6.4
Sex (%)		
Females	81,844 (62.9)	16,761 (62.5)
Males	48,207 (37.1)	10,055 (37.5)
Nordic, N (%)	122,480 (94.2)	25,930 (96.7)
Calendar year		
-1989	16,241 (12.6)	3481 (13.0)
1990-99	53,407 (41.1)	11,029 (41.1)
2000-	60,223 (46.3)	12,306 (45.9)
Socioeconomic status		
9 years of primary school	34,457 (26.5)	7076 (26.4)
2 years of high school	27,138 (20.9)	5610 (20.9)
3-4 years of high school	27,112 (20.8)	5546 (20.7)
College/university	38,655 (29.7)	7877 (29.4)
Missing	2689 (2.1)	707 (2.6)
Censored before end of follow-up		
Death	8416 (5.8)	2230 (7.7)
Emigration	1789 (1.2)	205 (0.7)
Type 2 diabetes [§]	3919 (3.0)	818 (3.1)
Autoimmune thyroid disease [§]	2140 (1.6)	1302 (4.9)
Drug use [§]		
Amiodarone	139 (0.1)	25 (0.1)
Corticosteroids	12,836 (9.9)	3776 (14.1)
Methotrexate	811 (0.6)	262 (1.0)
Tamoxifen	404 (0.3)	67 (0.2)
Tetracycline	17,487 (13.4)	4382 (16.3)
Lipid lowering drugs	12,028 (9.2)	2423 (9.0)

*Ages were rounded to the nearest year.

[#]Follow-up time until diagnosis of NAFLD, death, emigration or December 31, 2009. In reference individuals follow-up also ended with small intestinal biopsy.

[§]For definitions see main text and appendix.

Results

The median age at CD diagnosis was 28 years (for reference individuals: 27 years at study entry) (Table 1), with 42.8% diagnosed in childhood. Some 87% of CD individuals were diagnosed in 1990 or later (Table 1), and 97% were born in the Nordic countries (Table 1). The median follow-up was 10 years.

The median age at NAFLD diagnosis was 51 years in CD patients and 55 years in reference individuals. Among CD individuals with an NAFLD diagnosis, the median duration until NAFLD was 5.2 years after CD diagnosis (reference individuals: 6.6 years since study entry).

Risk of future NAFLD

During 246,559 person-years of follow-up, 53 individuals with CD had a diagnosis of NAFLD (21/100,000 person-years). In

comparison, we identified 85 reference individuals with a NAFLD diagnosis during 1,488,413 person-years (6/100,000 person-years). This corresponded to a HR of 2.8 (95% CI 2.0–3.8; $p < 0.001$). HRs did not change with adjustment for country of birth, socioeconomic status and level of education (adjusted HR = 2.8; 95% CI 2.0–3.9; $p < 0.001$; Supplementary data).

The HRs differed by follow-up time with the highest risk immediately after CD diagnosis. CD was associated with a 4.2-fold increased risk of NAFLD in the first five years after diagnosis (Table 2). This excess risk was to a large extent due to NAFLD diagnosed in the first year after CD diagnosis (HR for NAFLD = 13.3; 95% CI 3.5–50.3). Of 25 individuals with CD who had a diagnosis of NAFLD in the first five years after diagnosis, 8 were diagnosed within the first year after biopsy (compared to 9/66 reference individuals who had a diagnosis of NAFLD in the first five years after study entry). Excluding the first year of follow-up, the HR for NAFLD diagnosis for those with CD was

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Table 2. Relative risk of NAFLD based on follow-up time in individuals with celiac disease.

Follow-up after CD diagnosis (years)	CD: observed events	CD: expected events	HR; 95% CI	p value
<1	8	<1	13.3; 3.5-50.3	<0.001
<5	25	6	4.2; 2.5-7.2	<0.001
5-9.99	9	7	1.3; 0.6-2.8	0.459
10-14.99	11	2	4.6; 2.0-10.6	<0.001
≥15	8	3	2.5; 1.0-5.9	0.043

HR, Hazard ratio; CI, Confidence interval.
Reference is general population comparator cohort.

2.5 (95% CI 1.8–3.7). The HR for NAFLD more than 15 years after CD diagnosis was also 2.5 (95% CI 1.0–5.9; $p = 0.043$). When we restricted our data to individuals entering the study on Jan 1, 1997 or later, the HR for NAFLD was 3.6 (95% CI 2.3–5.6).

Overall HRs for NAFLD were higher in males (4.5; 95% CI 2.7–7.6) than in females (2.1; 95% CI 1.3–3.2) (Table 3), but the difference did not reach statistical significance (p for interaction = 0.126). The relative risk of NAFLD also seemed higher in individuals diagnosed with CD in childhood (HR 4.6; 95% CI 2.3–9.1) compared to a 2-fold increased risk among individuals with a CD diagnosis from age 40 years or later, but neither attained statistical significance (p for interaction with age at CD diagnosis was 0.059). Risk estimates were independent of calendar period (p for interaction = 0.317). The HR for NAFLD in individuals diagnosed with CD in the latest calendar period (2000–2008) was 4.1 (95% CI 2.4–7.0).

Sensitivity analyses

Using the attained age as the time scale did not influence our risk estimate (HR for NAFLD = 2.8; 95% CI 2.0–3.9). Adjusting for type 2 diabetes, autoimmune thyroid disease, lipid treatment and other drugs previously linked to NAFLD did not influence the risk estimate (adjusted HR = 2.7; 95% CI 1.8–4.0).

Prior NAFLD and later CD

Forty-seven individuals with CD (0.3%) and 46 matched controls (0.1%) had a diagnosis of NAFLD before the first biopsy showing CD, or before study entry for controls. This corresponded to an odds ratio (OR) of 3.9 (95% CI 2.8–5.5; $p < 0.001$). Adjustment for education, socioeconomic status and country of birth did not influence the risk estimate (adjusted HR = 3.8; 95% CI 2.7–5.4). The positive association was to a large part explained by an 8.6-fold increased risk of CD in the first year following NAFLD diagnosis (95% CI 5.5–13.3), followed by a moderate increase thereafter (OR 1.6; 95% CI 0.9–3.1). There were insufficient cases of CD diagnosed more than 5 years after NAFLD diagnosis to calculate a meaningful risk estimate (95% CI 0.0–362).

Alcohol-related liver disease in those with and without CD

In a post hoc analysis, where we included individuals with alcohol-related diagnoses (otherwise excluded in all analyses to minimize misclassification of NAFLD), we examined the

Table 3. Relative risk of NAFLD in relation to characteristics of patients with celiac disease.

Subgroup	CD: observed events	CD: expected events	HR; 95% CI
Sex			
Males	25	6	4.5; 2.7-7.6
Females	28	13	2.1; 1.3-3.2
Age (yr)			
<20	15	3	4.6; 2.3-9.1
20-39	14	4	3.7; 1.9-7.1
40-59	15	7	2.0; 1.1-3.6
60+	9	4	2.1; 1.0-4.5
Calendar period			
-1989	7	3	2.3; 0.9-5.6
1990-1999	25	11	2.3; 1.4-3.6
2000-2008	21	5	4.1; 2.4-7.0

HR, Hazard ratio; CI, Confidence interval.
Reference is general population comparator cohort.

proportion of individuals with fatty liver who also had an alcohol-related liver disease. In CD patients with NAFLD, 12% (10/82) had an alcohol-related liver disease vs. 15% (18/121) of controls with NAFLD.

Additional post hoc analyses

Marsh 1–2 CD was also associated with an increased risk of NAFLD (HR = 4.7; 95% CI 3.2–6.8).

Discussion

This nationwide study of more than 26,000 patients with CD found an increased risk of NAFLD in both children and adults with CD. The relative risk was highly increased in the first year of follow-up, but remained statistically significant even 15 years after CD diagnosis. In addition, those with a prior diagnosis of NAFLD appear to be at increased risk for a later diagnosis of CD. The prominent relative risk in the early years after diagnosis suggests a surveillance bias. This is not unexpected because one disease diagnosis or evaluation may lead to detection of the second disease.

NAFLD risks in CD

NAFLD has been predominantly linked to obesity [5,28], hyperlipidemia [5,28], and insulin resistance [5], though NAFLD can occur in those with a normal body mass index (BMI) [8]. The prevalence of CD among patients with NAFLD has been reported as 2.2–7.9% [29,30] and among these patients BMI was often in the normal range [29]. Conversely, little is known of the risks of NAFLD in those already diagnosed with CD. The observed increased incidence of NAFLD in our study population is interesting in that it suggests increased metabolic risks in CD patients occurring with treatment or the involvement of other non-metabolic mechanisms for the onset of NAFLD.

Dyslipidemia requiring pharmacotherapy and type 2 diabetes did not appear to contribute to NAFLD risk in this study.

Individuals with CD appear to have a decreased risk of type 2 diabetes even when controlling for BMI [31]. However, serum lipids may increase following treatment for CD.

The precise pathogenesis of NAFLD in CD is unclear. Some have speculated that cellular stress induced in CD patients may trigger the onset of NAFLD [32]. Intestinal permeability is increased in CD [33] as well as in NAFLD [17,34], and SIBO, known to be increased in both CD [20] and in NAFLD [17,18], may alter intestinal permeability [35]. Furthermore, increased intestinal permeability has been suggested as a potential trigger for the development of NASH in patients with hepatic steatosis. TNF- α , which mediates injury in CD and is increased in individuals with NASH [18], is believed to mediate the effects of endotoxin [36], potentially causing injury in those with NAFLD to induce NASH. Clarifying the relationship between NAFLD and CD is important in order to identify a potentially avoidable and treatable cause of liver disease among individuals with CD.

Strengths and limitations

The major strength of this study is the large number of patients with CD ($n = 26,816$) and the population-based nature of the study. In contrast with some older studies on comorbidities in CD [14], we did not rely on inpatient data to identify our exposure variable (CD). This is important since inpatient care is not routine for the diagnosis of CD. Our earlier research has shown that complications are more frequent in individuals hospitalized due to their CD than in those identified through biopsy record data (for instance the HR for tuberculosis was 3.7 in inpatients with CD [37] compared with 2.0 in CD patients identified through biopsy records [38]). We used biopsy reports from all of Sweden's pathology departments to identify CD giving a high sensitivity for diagnosed CD (during the study time, 96–100% of all adult gastroenterologists and pediatricians report performing a biopsy before assigning a diagnosis of CD to the patient) [27].

Biopsy report data on morphology were based on a mean of three tissue specimens [23], and this should identify approximately 95% of all CD. VA also has a high positive predictive value (also 95%) for CD in a Swedish cohort [27]. Although we are unaware of any study examining the validity of NAFLD in the Swedish Patient Registry, Carsjö *et al.* have earlier found that 87% of individuals with a recorded diagnosis of chronic liver disease or liver cirrhosis in 1986 had a correct diagnosis, and 88% in patients diagnosed in 1990 [39].

In addition to the large number of study participants, another strength is the long follow-up. These two factors allowed us to calculate risk estimates for NAFLD even 15 years after CD diagnosis, and to perform important subgroup analyses.

We acknowledge a number of weaknesses. We cannot rule out that a number of reference individuals have undiagnosed CD. This is, however, unlikely to influence our HRs since the overall prevalence of CD in Sweden is 1–2% [40], and less than 1 in 50 reference individuals should then have CD. If any, such misclassification is likely to decrease our HR for NAFLD somewhat and cannot explain the positive association seen in our study. Additionally, we acknowledge that the Patient Registry may have missed cases of NAFLD. One approach to increase the sensitivity for NAFLD would have been to identify individuals with unexplained chronic liver enzyme elevation accompanied by metabolic features. Unfortunately the Swedish ICD-10 system does not allow for this.

Given that the diagnosis code for NAFLD was not issued prior to 1997, there may be an underestimation of the early risk of NAFLD in individuals with CD diagnosed before this time. However, this would not diminish the early risk seen in those diagnosed in later years. Additionally, the follow-up strata used in our statistical design ensured that those diagnosed with NAFLD in 1998 (once the ICD-10 code K76.0 came into use) contributed to the risk increase in the follow-up stratum from 1982 to 1998, potentially leading to a minimal increase in risk estimates of NAFLD development after CD diagnosis, but would not have falsely increased risk estimates of NAFLD in the early years following CD diagnosis.

While overweight and obesity are common in CD, Swedish registers do not contain individual-based data on BMI. Nor is obesity generally recorded in the Patient Registry. In general, CD patients have a lower BMI before CD diagnosis than after [41], but we cannot rule out that adjustment for BMI would have influenced our risk estimates. We tried to minimize misclassification of NAFLD through excluding patients with a diagnosis of alcohol-related disease. Unfortunately Swedish National Registries lack data on individual alcohol consumption and we were therefore unable to confirm that individuals classified as having NAFLD did not, in fact, have an alcohol consumption >20 – 30 g/day [42]. While this is a major shortcoming of our study, Sweden has a low per capita alcohol consumption [43] and NAFLD is generally much more common than alcohol-related fatty liver disease. Given that alcohol consumption is not regarded as positively associated with CD, the kind of misclassification that may occur in this study (NAFLD that is in fact alcohol-related) is therefore most likely to dilute associations and will not explain the positive association between CD and NAFLD seen in our study. Nevertheless, this is a major shortcoming of our study and while we may infer that the potential for such misclassification had no bearing upon our findings, this cannot be said for certain.

Finally, our measure of NAFLD (inpatient or hospital-based outpatient diagnosis) may have a low sensitivity of NAFLD. Many patients with NAFLD are unaware of their condition and do not seek healthcare. This may lead to an underestimate of NAFLD in our cohort. In addition, given the large-scale nature of this study, it is impossible to confirm how individual diagnoses of NAFLD were rendered, or if these diagnoses were appropriately assigned. Additionally, we were unable to examine the association between CD and undiagnosed NAFLD. Neither were we able to examine NAFLD appearance according to Marsh stages since the Swedish National Registries do not contain any data on histopathology.

Lastly, surveillance bias may have influenced our findings. Individuals with CD were likely followed more carefully than those in the general population, and this may have increased NAFLD diagnoses in CD patients. However, even prior to diagnosis with CD, the odds of a NAFLD diagnosis were significantly greater (OR 3.9) among those with a later diagnosis of CD versus those without a CD diagnosis. Whether this is due in part to evaluation of the patients' compliance prior to the CD diagnosis cannot be determined. However, these limitations are inherent in such a large-scale study.

Mechanisms

Of importance, the risk of NAFLD was also increased among individuals with Marsh 1–2 histology. Although these are results

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of a post hoc analysis, the findings are nevertheless intriguing. While many individuals with true CD do show Marsh 1–2 lesions, Marsh 1–2 may also reflect many non-CD conditions [44]. Among potential explanations are the lack of treatment with a gluten-free diet (in a patient chart validation we have previously found that only 2/39 (5%) randomly selected individuals with Marsh 1–2 had been advised to adhere to a gluten-free diet [27]), that Marsh 1–2 represent other forms of inflammation/autoimmunity with even stronger links to NAFLD than CD, and surveillance bias or confounded by indication. Finally patients with Marsh 1–2 may share common risk factors with NAFLD.

We cannot rule out that some small intestinal biopsies in our study were carried out due to unrecorded liver disease prior to CD. Against this argues that we found a high risk of NAFLD in CD in the last calendar period when we had the greatest coverage of liver disease since the Swedish Patient Registry began registering also hospital-based outpatient visits in 2001.

Although the difference in NAFLD risk estimates between age groups did not attain statistical significance, we speculate that the higher risk in children (4-fold increase) is due to fewer competing factors and comorbidities, and lower risk of misclassification. Although we tried to exclude alcohol-induced fatty liver, we cannot rule out that some NAFLD cases were due to alcohol intake in older people, but less likely so in younger study participants. Hence, it is possible that misclassification of NAFLD has diluted the true association with CD and underestimated the HR for NAFLD especially in older individuals.

Conclusion

In conclusion, individuals with CD seem to be at an increased risk of NAFLD compared to the general population, a risk that diminishes in magnitude, but persists over the long term. These findings should be confirmed in a population of NAFLD patients where excess alcohol intake has been ruled out and the diagnosis has been confirmed through liver biopsy.

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Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Authors' contributions

ICMJE criteria for authorship read and met: NR, BL, RH, PG, JFL. Agree with the manuscript's results and conclusions: NR, BL, RH, PG, JFL. Designed the experiments/the study: NR, JFL.

Collected data: JFL. Analyzed the data: JFL. Wrote the first draft of the paper: NR and JFL. Contributed to study design, interpretation of data and writing: BL, RH, PG. Interpretation of data; approved the final version of the manuscript: NR, BL, RH, PG, JFL. Responsible for data integrity: JFL. Obtained funding: JFL.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.jhep.2015.01.013>.

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