

Celiac Disease and Anorexia Nervosa: A Nationwide Study

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abstract

BACKGROUND AND OBJECTIVE: Previous research suggests an association of celiac disease (CD) with anorexia nervosa (AN), but data are mostly limited to case reports. We aimed to determine whether CD is associated with the diagnosis of AN.

METHODS: Register-based cohort and case-control study including women with CD ($n = 17\,959$) and sex- and age-matched population-based controls ($n = 89\,379$). CD (villous atrophy) was identified through the histopathology records of Sweden's 28 pathology departments. Inpatient and hospital-based outpatient records were used to identify AN. Hazard ratios for incident AN diagnosis were estimated by using stratified Cox regression with CD diagnosis as a time-dependent exposure variable. In the secondary analyses, we used conditional logistic regression to estimate odds ratios for being diagnosed with AN before CD.

RESULTS: Median age of CD diagnosis was 28 years. During 1 174 401 person-years of follow-up, 54 patients with CD were diagnosed with AN (27/100 000 person-years) compared with 180 matched controls (18/100 000 person-years). The hazard ratio for later AN was 1.46 (95% confidence interval [CI], 1.08–1.98) and 1.31 beyond the first year after CD diagnosis (95% CI, 0.95–1.81). A previous AN diagnosis was also associated with CD (odds ratio, 2.18; 95% CI, 1.45–3.29). Estimates remained largely unchanged when adjusted for socioeconomic characteristics and type 1 diabetes.

CONCLUSIONS: The bidirectional association between AN diagnosis and CD warrants attention in the initial assessment and follow-up of these conditions because underdiagnosis and misdiagnosis of these disorders likely cause protracted and unnecessary morbidity.

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WHAT'S KNOWN ON THIS SUBJECT: Case reports suggest an association of celiac disease with anorexia nervosa, but there are few large-scale studies. This is additionally complicated by the clinical similarities between the illnesses that may lead to misclassification, delay in diagnosis, and improper treatment.

WHAT THIS STUDY ADDS: This study of some 18 000 women with celiac disease (CD) showed a positive association between CD and anorexia nervosa both before and after CD diagnosis. This bidirectional association warrants attention in the initial medical assessment and follow-up of these conditions.

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Celiac disease (CD) is an inflammatory disorder in which gluten ingestion causes small-intestinal villous atrophy; the treatment consists of a lifelong strict adherence to a gluten-free diet.¹ The disease occurs in 1% to 2% of the Western population² and is more prevalent in women. Common presenting symptoms include gastrointestinal complaints, loss of appetite, fatigue, and, in children, stunted growth and pubertal delay.³ There are also numerous extraintestinal manifestations of CD, including psychiatric comorbidity.⁴

Anorexia nervosa (AN) is an eating disorder associated with underweight, fear of weight gain, and disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight on self-evaluation, or persistent lack of recognition of the seriousness of the low weight.⁵ The disorder typically affects girls during adolescence and young adulthood and is associated with elevated psychiatric and somatic morbidity and mortality.⁶ Diseases with dietary constraints, such as food allergy and type 1 diabetes,^{7,8} have been associated with AN. It is conceivable that a restrictive diet, in susceptible individuals, may trigger obsessive eating patterns; for others, the diet may cause a prolonged negative energy balance that could be the tipping point for developing AN.⁹ Previous research has indicated that AN may be linked to CD, but data have mostly been limited to case reports.^{10–16} The only earlier population-based study in this field found CD to be associated with a significant two-to-threefold increased diagnosis of AN and vice versa.¹⁷ However, that study was restricted to patients requiring hospital admission for CD and may therefore have included patients with a high degree of comorbidity, which may have caused exaggerated risk estimates.

The primary aim of this nationwide study was to test the hypothesis that individuals with biopsy-verified CD were at increased risk of AN before or after CD diagnosis. Our secondary aim was to examine if any observed association with AN diagnosis was specific to CD or also present in patients with milder small-intestinal histopathology. We therefore examined the association of diagnosed AN also among biopsied individuals without CD.

METHODS

Using the personal identity number¹⁸ assigned to all Swedish residents, we linked histopathology data on individuals undergoing small-intestinal biopsy to the National Patient Register¹⁹ to determine their risk for AN diagnosis compared with population-based matched controls.

Study Sample

Individuals with CD, defined as the presence of small-intestinal villous atrophy (Marsh grade III),²⁰ were identified by using the computerized histopathology records of Sweden's 28 pathology departments; an earlier evaluation has shown that 95% of Swedish individuals with villous atrophy have a clinical CD diagnosis.²¹ The time of diagnosis was defined as the time of small-intestinal biopsy, ranging from 1969 to 2008.¹⁸

We also identified individuals undergoing biopsy showing small-intestinal inflammation (Marsh grade I–II) or normal mucosa (Marsh grade 0) but with a positive CD serology test (antigliadin, antiendomysial, or transglutaminase antibodies).²² Data on CD serology originated from 8 university hospitals providing care for approximately half of the Swedish population.²²

By using the same dataset as previously reported,²³ this study restricted participation to women

living in Sweden in 1987 and later: 17 959 with CD, 7455 with small-intestinal inflammation, and 2307 women with normal small-intestinal mucosa, but positive CD serology. Through the government agency Statistics Sweden, each individual undergoing biopsy was matched by sex, age, calendar period of birth, and county of residence with up to 5 controls from the general population ($n = 137\,818$) (Fig 1). Our main analyses were restricted to women to eliminate wrongful AN diagnoses in men.

Anorexia Nervosa

Diagnosis of AN was defined^{24,25} by any of the following International Classification of Diseases, Eighth Revision (ICD-8), International Classification of Diseases, Ninth Revision (ICD-9), and International Classification of Diseases, Tenth Revision (ICD-10) codes recorded in the National Patient Register: ICD-8, 306.50; ICD-9, 307B; ICD-10, F50.0 and F50.1. To eliminate diagnostic misclassification from eating-related disorders of young children, we restricted AN to diagnoses recorded at age 6 years or later.²⁶ The National Patient Register started in 1964, became nationwide in 1987, and includes hospital-based outpatient care since 2001.¹⁹ The date of diagnosis was determined by the first appearance of an AN diagnosis.

Covariates

We obtained data from Statistics Sweden on the highest attained education level and socioeconomic status until the end of 2009; for children, we used the highest category attained by their parents. Socioeconomic status was defined by occupational status according to the European Socioeconomic Classification system.²⁷ We also retrieved information on type 1 diabetes diagnosis as recorded in the National Patient Register by age

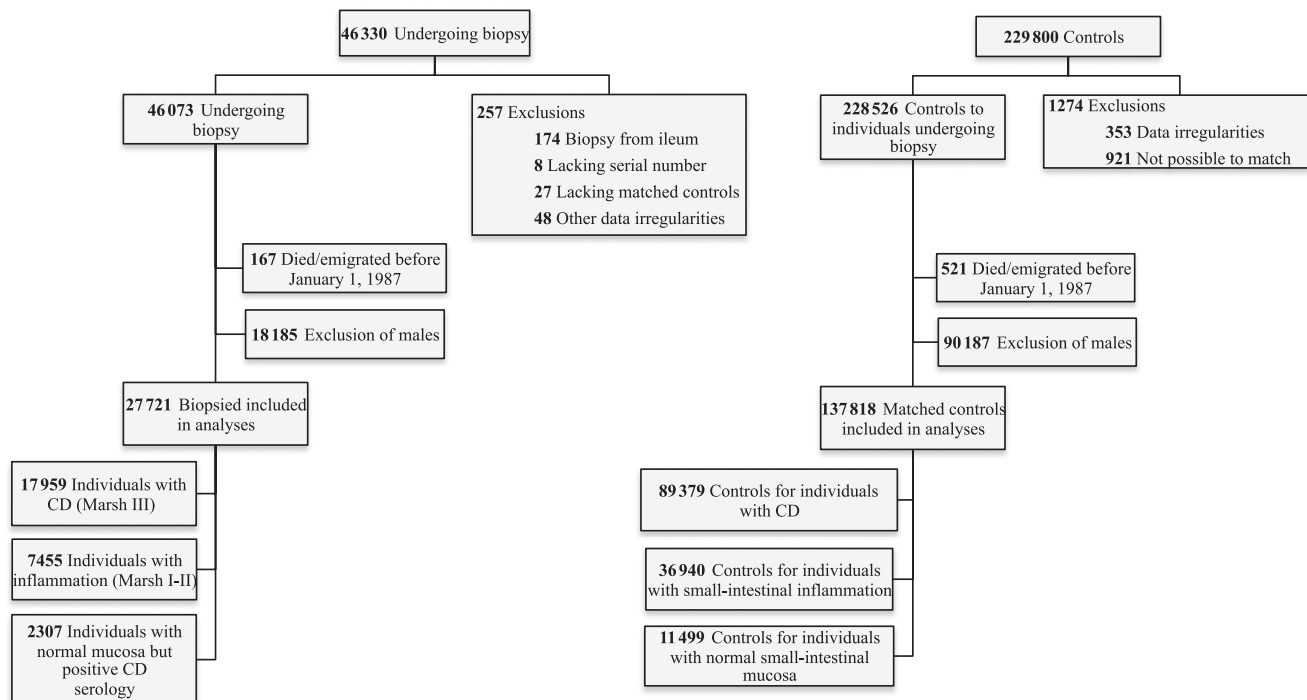


FIGURE 1

Flowchart illustrating the formation of the study sample. Individuals undergoing small-intestinal biopsy were identified by using the computerized histopathology records of Sweden's pathology departments. The study sample was restricted to women living in Sweden in 1987 (when the National Patient Register became nationwide) and later.

TABLE 1 Characteristics of Women Undergoing Small-Intestinal Biopsy

	CD	Inflammation	Normal Mucosa With Positive CD Serology
Total	17 959	7 455	2 307
Year of birth, median (interquartile range)	1970 (1945–1989)	1951 (1933–1969)	1963 (1947–1978)
Age (y) at time of biopsy			
Median (interquartile range)	28 (6–52)	46 (31–63)	38 (23–53)
Age 0–19, n (%)	7428 (41)	717 (10)	459 (20)
Age 20–39, n (%)	3649 (20)	2196 (29)	755 (33)
Age 40–59, n (%)	3862 (22)	2304 (31)	740 (32)
Age 60+, n (%)	3020 (17)	2238 (30)	353 (15)
Calendar year at time of biopsy			
Median (interquartile range)	1999 (1993–2003)	2000 (1994–2004)	2001 (1998–2004)
≤1986, n (%)	1210 (7)	464 (6)	0 (0)
1987–1999, n (%)	8601 (48)	3238 (43)	819 (36)
≥2000, n (%)	8148 (45)	3753 (50)	1488 (64)
Type 1 diabetes ^a , n (%)	526 (3)	59 (1)	35 (2)

Histopathology findings indicating CD (villous atrophy, Marsh III), inflammation (Marsh I–II), and normal mucosa (Marsh 0), but with positive CD serology 180 days before and until 30 days after biopsy (antigliadin, antiendomysial, or antitransglutaminase antibodies). Controls are not included in the table because their age, sex, and calendar year distributions were identical to those of the individuals undergoing biopsy (due to matching).

^a Type 1 diabetes as recorded in the National Patient Register by age 30 years (ICD-8/ICD-9, 250; ICD-10, E10).

30 years (ICD-8/ICD-9, 250; ICD-10, E10). We used an age cutoff because ICD-8 and ICD-9 do not distinguish between type 1 and type 2 diabetes. Covariates are categorized as shown in Table 1.

Statistical Analyses

The associations of the diagnosis of AN were estimated by using Cox regression and logistic regression models for matched data.

Cox Regression: Subsequent Diagnosis of AN After CD

We used stratified Cox proportional-hazards regression, with age in days as the time metric, to estimate hazard ratios (HRs) for incident diagnosis of AN with associated 95% confidence intervals (CIs). The HRs were modeled separately within each stratum consisting of 1 woman undergoing biopsy and up to 5 matched controls; this stratumwise analysis eliminates the effect of the matching variables (ie, age, sex, calendar period of birth, and county of residence). Individuals were followed from January 1, 1987, or birth for children born thereafter, until AN diagnosis, emigration, death, or December 31, 2009, whichever occurred first. The follow-up started in 1987, when the National Patient Register became nationwide, for all participants at risk for AN. We excluded 73 individuals diagnosed with AN before 1987 (start of follow-up) and 319 with a record

of AN before undergoing biopsy (or corresponding date among controls). Hence, the Cox regression analyses included 17 924 individuals with CD, 7425 with inflammation, 2294 with normal mucosa but positive CD serology, and 137 504 matched controls.

The proportional-hazards assumption was found to be valid based on graphical presentation of the data. The time of biopsy (and corresponding date for matched controls) was included as a time-dependent variable; individuals with CD, inflammation, or normal mucosa but positive CD serology were defined as exposed from time of biopsy and thereafter considered exposed throughout follow-up. Individuals biopsied before January 1, 1987 were considered to be exposed from the start of the follow-up period. Hazard ratios were adjusted for education level, socioeconomic status, and type 1 diabetes.

For individuals with CD and their controls, we conducted separate analyses for children (age ≤ 19 years) and adults and by calendar period of biopsy (≤ 1994 and ≥ 1995). The HR for AN beyond the first year of CD diagnosis was modeled by introducing a 1-year lag time during which an individual was considered unexposed until 1 year after diagnosis and exposed thereafter. To test the ascertainment of AN, we performed a separate analysis restricted to AN listed as the main diagnosis in the National Patient Register.

Logistic Regression: Diagnosis of AN Before CD

We used conditional logistic regression to estimate odds ratios (ORs) for previous diagnosis of AN among individuals undergoing biopsy compared with their matched controls.²⁸ Analyses were performed stratumwise and therefore conditioned on age, sex,

calendar period of birth, and county of residence. In parallel with the above, we performed adjusted analyses, accounting for education level, socioeconomic status, and type 1 diabetes. In individuals with CD and their controls, we also performed analyses stratified by age and calendar year of birth.

In a post hoc analysis, we also examined AN and CD in men (CD, $n = 11\ 025$; controls, $n = 54\ 774$).

Statistical significance was defined as 95% CIs for HRs and ORs not including 1.00. Data were analyzed by using Stata version 14 (Stata Corp, College Station, TX).

Ethics

This study was approved by the Regional Ethical Vetting Board in Stockholm, Sweden, which deemed that individual informed consent was not required.²⁹ Data used in this study were deidentified.

RESULTS

Among the 17 959 women with CD in this study, the median age at CD diagnosis was 28 years (interquartile range, 6–52 years) (see Table 1 for population characteristics). There were 353 individuals diagnosed with AN at a median age of 17 years (interquartile range, 15–22 years).

CD and Future AN Diagnosis

From 1987 through 2009, during 1 174 401 person-years of follow-up, 54 patients with CD were diagnosed with AN compared with 180 matched controls. The incidence rate for AN after a CD diagnosis was 27/100 000 person-years (95% CI, 21–36) compared with 18/100 000 person-years (95% CI, 16–21) among matched controls; this corresponded to an HR for AN diagnosis of 1.46 (95% CI, 1.08–1.98). Adjustments for education level, socioeconomic status, and type 1 diabetes yielded a largely unchanged HR (Fig 2). Analyses stratified by age at CD

diagnosis and by calendar period of biopsy are presented in Fig 2. Among women with a main diagnosis of AN in the National Patient Register, the HR was 1.34 (95% CI, 0.97–1.86).

Diagnosis of AN Before CD

A total of 33 individuals with CD (0.18%) and 76 matched controls (0.09%) had a record of AN before CD diagnosis (and corresponding date among controls); the OR for a previous diagnosis of AN was 2.18 (95% CI, 1.45–3.29) among individuals diagnosed with CD compared with controls. There were significantly increased ORs for a previous history of AN when stratifying by age at CD diagnosis and calendar period of diagnosis (Fig 3). When restricting our analysis to those with AN listed as the main diagnosis in the National Patient Register, the OR was 2.13 (95% CI, 1.37–3.32).

AN in Biopsied Patients Without CD

In secondary analyses, we tested the association of AN with (1) small-intestinal inflammation without villous atrophy and (2) normal small-intestinal mucosa, but with positive CD serology. Both groups had a significantly increased risk for diagnosis of AN before as well as after the time of biopsy compared with matched controls (Tables 2 and 3).

Post hoc Analysis: AN and CD in Men

There was no significantly increased risk for subsequent AN among males with CD (HR, 0.95; 95% CI, 0.21–4.32). This HR was based on 12 men being diagnosed with AN. Nor did we find a significantly increased OR for previous AN among men with CD (OR, 2.50; 95% CI, 0.63–10.00).

DISCUSSION

This nationwide study found a positive association between CD and AN both before and after

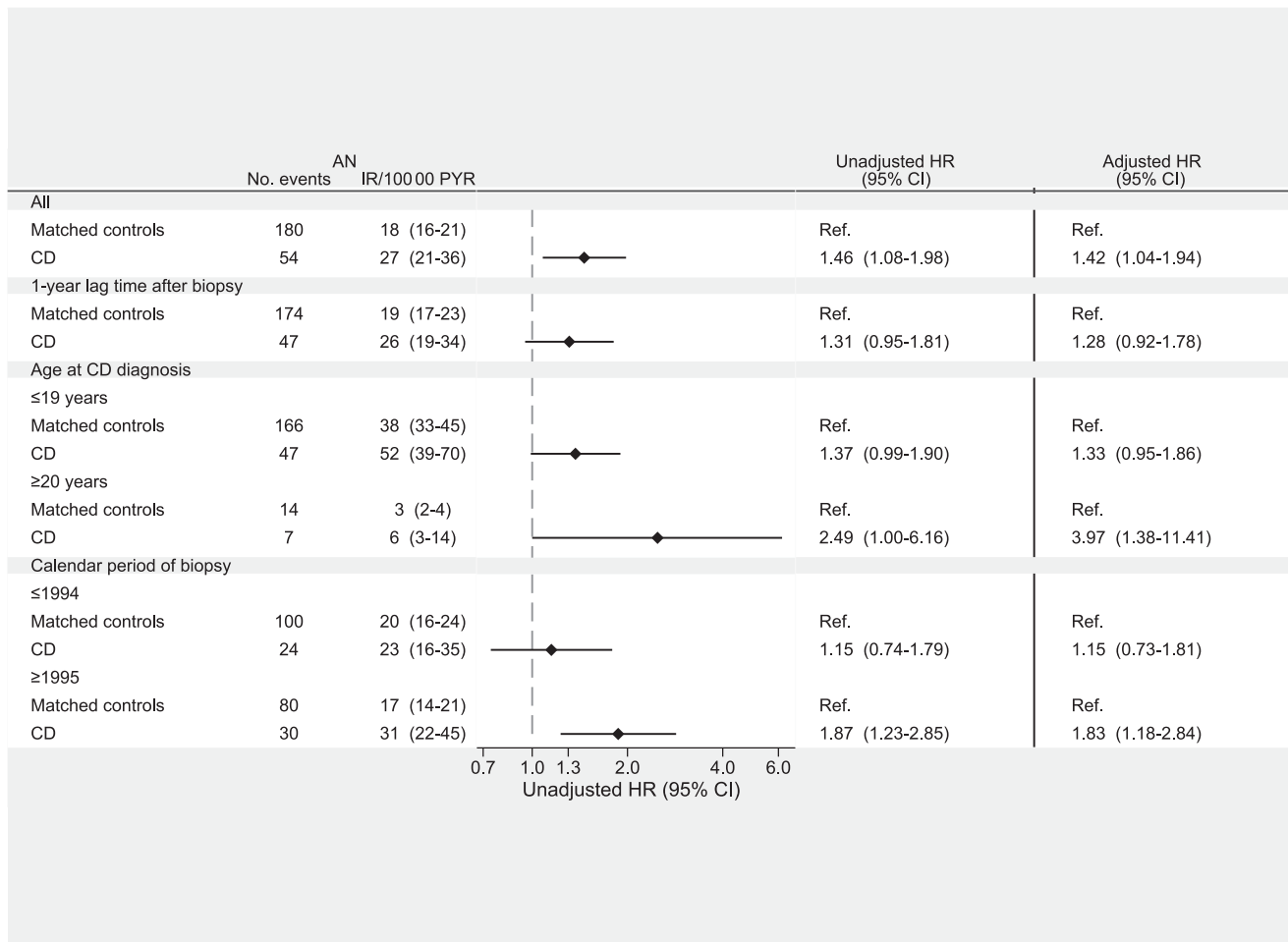


FIGURE 2

HR for AN after CD diagnosis. Participants were matched for age, sex, calendar period of birth, and county of residence; adjusted analyses accounted for education level, socioeconomic status, and type 1 diabetes. IR, incidence rate; PYR, person-years; Ref, reference.

CD diagnosis. This bidirectional association should encourage physicians to closely monitor these patients and calls for heightened understanding of factors that contribute to their cooccurrence.

Potential Mechanisms of Action

We propose that a number of factors may contribute to this bidirectional association.

First, on initial examination, individuals with underlying CD or AN may be misdiagnosed with the other condition. In patients who receive an initial erroneous CD diagnosis, it should soon become evident that the gluten-free diet is not effective and additional

evaluation would reveal the eating disorder. In patients who receive an initial erroneous diagnosis of AN and who present with ongoing symptoms of fatigue and abdominal complaints, additional workups should be initiated to rule out CD or other gastrointestinal illnesses. Such persistent symptoms should be followed up because untreated CD leads to complications and a poorer quality of life.⁴

Second, we cannot rule out that our results have been influenced by surveillance bias. Before and after the time of diagnosis, individuals with either CD or AN are typically more extensively investigated for other diseases compared with individuals in the general

population. For example, diarrhea due to laxative misuse in AN as well as liver enzyme abnormalities can both lead to a work-up for CD. The positive associations found between AN and small-intestinal inflammation but no villous atrophy and with having a biopsy with normal mucosa but positive CD serology strongly indicate that surveillance bias at least partly plays a role here because, in Sweden, a gluten-free diet is not typically recommended for these conditions.

Third, shared risk factors, including genetic susceptibility, may play a role.³⁰ Recent genomewide association studies of AN have indicated genetic regions shared

TABLE 2 Association of Future AN Diagnosis Among Biopsied Women Without CD

	No. of Incident AN	Incidence Rate of AN per 10 000 PYR	HR for Future AN ^a	
			Unadjusted HR for Future AN (95% CI)	Adjusted ^b HR for Future AN (95% CI)
Matched controls	20	6 (4–9)	Ref	Ref
Inflammation ^c	9	13 (7–25)	2.12 (0.97–4.67)	1.41 (0.55–3.58)
Matched controls	19	20 (13–31)	Ref	Ref
Normal mucosa but CD+ serology ^d	9	47 (24–90)	2.45 (1.10–5.45)	2.59 (1.10–6.10)

PYR, person-years; Ref, reference.

^a HRs were estimated by using stratified Cox proportional-hazard regression and ORs were estimated with conditional logistic regression. Controls were matched for age, sex, calendar period of birth, and county of residence.

^b Adjusted analyses accounting for education level, socioeconomic status, and type 1 diabetes.

^c Small-intestinal inflammation without villous atrophy (Marsh I–II).

^d Normal mucosa (Marsh 0) but with positive CD serology 180 days before and until 30 days after biopsy (antigliadin, antiendomysial, or antitransglutaminase antibodies).

with type 1 diabetes and other autoimmune illnesses. Together with other population-based data,^{17,31} these results encourage

a closer examination of the genetic relationship between AN and autoimmune gastrointestinal diseases.

Clinical Relevance

The positive association of CD with AN, both before and after CD diagnosis, should spur a careful initial assessment and follow-up of these illnesses. It should also be appreciated that the 2 conditions can complicate each other. Having AN makes it harder to follow a gluten-free diet, and it cannot be excluded that some AN patients knowingly consume gluten-containing products to lose weight.¹¹ The treatment of AN and CD require different competences and a multidisciplinary approach to management is important.

Although the vast majority of AN occurs in women, this disease can also occur in men. Although we

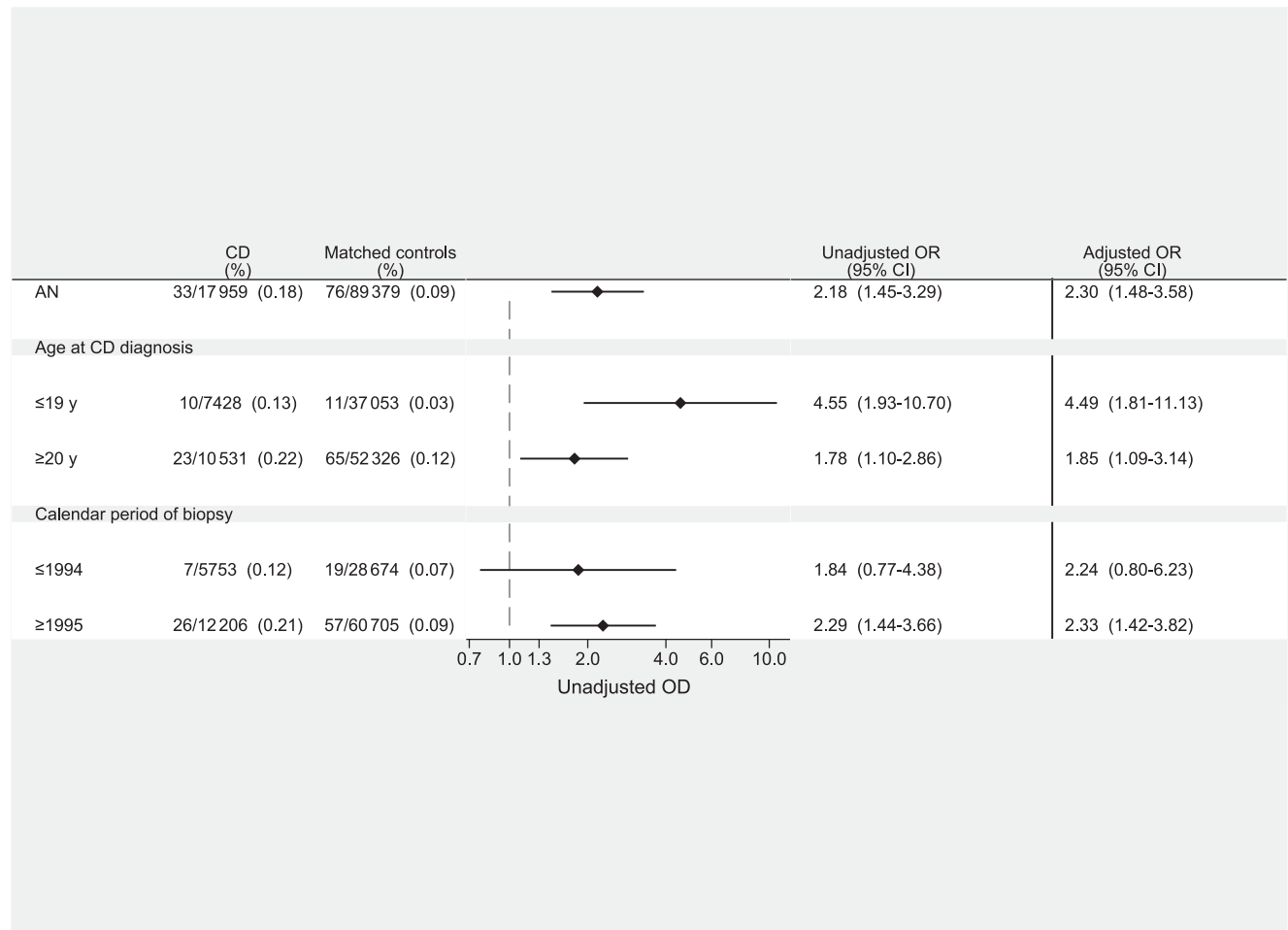


FIGURE 3

OR for AN before CD diagnosis. Participants were matched for age, sex, calendar period of birth, and county of residence. Adjusted analyses accounted for education level, socioeconomic status, and type 1 diabetes.

TABLE 3 Association of AN Diagnosis Among Biopsied Women Without CD, Odds Ratio for Prior AN

	OR for Previous AN ^a			
	Undergoing Biopsy (%)	Matched Controls (%)	Unadjusted OR for Previous AN (95% CI)	Adjusted ^b OR for Previous AN (95% CI)
Inflammation ^c	30/7455 (0.40)	45/36940 (0.12)	3.35 (2.11–5.33)	3.39 (2.09–5.49)
Normal mucosa but CD+ serology ^d	13/2307 (0.56)	23/11499 (0.20)	2.86 (1.44–5.68)	3.22 (1.49–6.96)

^a HRs were estimated by using stratified Cox proportional-hazard regression and ORs were estimated with conditional logistic regression. Controls were matched for age, sex, calendar period of birth, and county of residence.

^b Adjusted analyses accounting for education level, socioeconomic status, and type 1 diabetes.

^c Small-intestinal inflammation without villous atrophy (Marsh I–II).

^d Normal mucosa (Marsh 0) but with positive CD serology 180 days before and until 30 days after biopsy (antigliadin, antiendomysial, or antitransglutaminase antibodies).

found no significant association between AN and CD in men, this does not mean that the risk of CD is different in women and men with AN. Our male-restricted analysis had low statistical power, and we urge caution when interpreting those findings.

Comparison With Earlier Literature

Research on CD and AN almost exclusively consists of case-series.^{10–15} The largest case series so far was published by Leffler et al¹¹ in 2007 and included 10 female patients with CD and eating disorders. All patients in this study were first diagnosed with AN or bulimia nervosa and only later with CD. Only 1 previous study by Basso et al¹⁶ specifically screened for CD in patients with AN; 1 out of 177 (0.6%) screened patients with AN had biopsy-verified CD, but this study was unable to calculate any relative risk estimates because it had no control group, nor did the investigators examine the temporality between CD and AN.

Recently, however, an English register-based study, including hospitalized AN patients, found a significant threefold increased risk of later CD diagnosis and a twofold risk increase for AN in CD patients.¹⁷ Although that study identified patients requiring hospital admission for CD, our study includes both in- and outpatients with CD. This distinction may be important because inpatient registers are often limited to patients

with more severe CD and more susceptible to surveillance bias, which could overinflate risk estimates.

Strengths and Limitations

The main strength of our paper is the population-based approach with almost 18 000 CD patients. The large numbers allowed us to examine subsets of patents with CD stratified by age and calendar period of diagnosis.

We used small-intestinal biopsy reports with villous atrophy to identify individuals with CD. Throughout the study period, biopsy was the gold standard for CD diagnosis, and >96% of Swedish pediatric and adult gastroenterologists performed a biopsy before assigning a CD diagnosis.²¹ Non-celiac causes for villous atrophy are uncommon in Sweden, and when we examined 114 randomly selected charts of patients with villous atrophy, 108 (95%) had CD.²¹ In a subset of patients with available data at the time of CD diagnosis, 88% were positive for either transglutaminase, endomysium, or antigliadin antibodies. Of note, a large proportion of patients in our sample were diagnosed when gliadin was the only available antibody and before transglutaminase and endomysium antibodies were readily available in the clinic.

Although we are unaware of any validation of AN as registered in the

National Patient Register (and we did not have access to medical records to verify the AN diagnoses), the overall validity of this register is high with 85% to 95% of diagnoses being correct.¹⁹ To increase the specificity of the AN diagnosis, we carried out a sensitivity analysis restricting our outcome to individuals with AN listed as the main diagnosis. This analysis also showed a positive association, although the HR was somewhat lower (1.34 vs 1.46 for our main analysis) and was not statistically significant.

This study has some limitations. We did not screen for undiagnosed CD or subthreshold AN. It is therefore likely that some individuals with long-standing eating disturbances were first screened for CD, and then subsequently diagnosed with AN only when the gluten-free diet did not help. A related limitation is our lack of clinical data on symptoms or signs that would enable us to differentiate between subtypes of AN or differences in CD presentation. Moreover, in patients with an initial diagnosis of AN followed by a subsequent diagnosis of CD, it is also possible that the AN diagnosis may represent a misdiagnosis of CD.

In our earlier validation study of CD,²¹ 1 in 3 patients with CD suffered from weight loss or growth failure, which are symptoms resembling AN. It is not likely that the association is due to gastrointestinal changes in AN patients being misinterpreted as CD on biopsy. Not even AN with severe underweight has demonstrated mucosal atrophy.^{10,32}

In addition, data on ethnicity and diet were lacking. The latter prevented us from studying whether strict adherence to a gluten-free diet mediated the association with AN. As part of an earlier validation study of our cohort, 71 out of 86 (83%) randomly selected patients with CD revealed dietary adherence according

to patient chart data.²¹ Hence, we cannot isolate a restricted diet as the mechanism underlying the association between CD and later AN; however, given the high adherence to gluten-free diets, we speculate that dietary restrictions may trigger AN in susceptible individuals.

Finally, we cannot rule out that residual confounding factors may have influenced our results, although we accounted for important potential confounders, such as age, birth year, country of residence, education,

socioeconomic status, and type 1 diabetes.

CONCLUSIONS

The bidirectional association between diagnosis of AN and CD warrants attention in the initial assessment and the follow-up of women with these illnesses. This is important because the presentation of these conditions may mimic each other and the misdiagnosis of either disorder likely causes protracted and unnecessary morbidity.

ABBREVIATIONS

AN: anorexia nervosa
CD: celiac disease
CI: confidence interval
HR: hazard ratio
ICD-8: *International Classification of Diseases, Eighth Revision*
ICD-9: *International Classification of Diseases, Ninth Revision*
ICD-10: *International Classification of Diseases, Tenth Revision*
OR: odds ratio

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