Increased risk of atrial fibrillation in patients with coeliac disease: a nationwide cohort study

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Aims
Inflammatory markers are established risk factors for atrial fibrillation (AF), but the role of autoimmune diseases is unknown. The aim of the study was to examine the association between coeliac disease (CD) and AF in a large cohort of patients with biopsy-verified CD.

Methods and results
We identified 28,637 patients with CD through biopsy reports (defined as Marsh 3: villous atrophy) from all pathology departments (n = 28) in Sweden. Biopsies had been performed between 1969 and 2008. Age- and sex-matched reference individuals (n = 141,731) were identified from the Swedish Total Population Register. Data on AF were obtained from the Swedish Hospital Discharge Register, the Hospital Outpatient Register, and the Cause of Death Register. Hazard ratios (HRs) for AF were estimated using Cox regression. In the CD cohort, 941 individuals developed AF (vs. 2,918 reference individuals) during a median follow-up of 9 years. The corresponding adjusted HR for AF was 1.34 (95% CI = 1.24–1.44). The absolute risk of AF in CD was 321 of 100,000 person-years, with an excess risk of 81 of 100,000. A prior AF diagnosis was also associated with an increased risk of subsequent CD (odds ratio = 1.45, 95% CI = 1.31–1.62).

Conclusions
Atrial fibrillation is more common both before and after CD diagnosis in patients with CD though the excess risk is small. Potential explanations for the increased risk of AF in CD include chronic inflammation and shared risk factors, but ascertainment bias may also have contributed.

Clinical implications
Coeliac disease affects 1–2% of the Western population. Our results indicate that patients with coeliac disease, verified by intestinal biopsy, are at increased risk of atrial fibrillation. This observation is consistent with previous findings that elevation of inflammatory markers predicts atrial fibrillation. Additional studies are needed to clarify the mechanistic link between atrial fibrillation and autoimmune diseases such as coeliac disease.

Keywords
Autoimmunity • Coeliac • Inflammation • Atrial fibrillation

Introduction
Coeliac disease (CD), commonly known as gluten intolerance, is an immune-mediated disorder that occurs in 1% of the Western world. In patients with CD ingestion of gluten causes small intestinal inflammation and villous atrophy (VA).

Atrial fibrillation (AF) is a growing public health problem associated with substantial morbidity and mortality through an increased risk of ischaemic stroke and heart failure.1,2 Elevation of inflammatory markers has consistently been shown to precede onset of AF.3–6 Hypothetically, inflammatory processes could result in atrial fibrosis, which is considered a substrate for AF.8 However, additional studies are desirable to identify the underlying causes of such inflammation.

There are limited data on the association of autoimmune diseases with AF.2 Although several studies suggest an increased risk of cardiovascular morbidity and mortality in CD,10,11 we are only aware of one study directly addressing the association...
between CD and AF. However, that study was underpowered regarding AF but indicated a positive relationship between CD and prior AF [odds ratio, OR = 1.26 (95% CI = 0.97–1.64)].

Thus, it remains unknown whether CD is associated with risk of AF. We therefore examined the risk of AF in a Swedish nationwide cohort study of more than 28 000 patients with biopsy-verified CD.

**Methods**

We collected nationwide data on CD through biopsy reports from all (n = 28) Swedish pathology departments. Using the unique personal identity number (PIN), these data were matched to both inpatient and outpatient data on AF in the Swedish National Patient Register and in the Swedish Cause of Death Register.

**Collection of biopsy data**

We defined our study exposure, CD, as having a small intestinal biopsy with VA.

**Villus atrophy**

Between October 2006 and February 2008, we identified 29 148 patients with CD through computerized biopsy reports from all of the 28 Swedish pathology departments. The biopsies had been performed from 1969 to 2008 (Table 1). We defined CD as having a SnoMed pathology code equal to VA and did not require a positive CD serology for the diagnosis (see Appendix for a list of Swedish SnoMed codes translated into the international histopathology grading system by Marsh). However, a study from our group has shown that 88% of individuals with VA and available serology data also had positive CD serology at the time of biopsy.

**Inflammation and normal mucosa**

We also collected data from biopsy reports in patients with small intestinal inflammation but no VA (Marsh 1–2; n = 13 446) and those with normal mucosa (Marsh 0; n = 244 992).

A regional subset of unique individuals with normal mucosa (121 952 of 244 992 patients) was matched against data on positive CD serology data (gliadin antibodies, endomysial antibodies, and tissue transglutaminase antibodies). Serology data originated from eight university hospitals where patients had undergone biopsy. These university hospitals are responsible for both rural and urban areas, representing 49% of the Swedish population. Linkage with CD was performed from 1969 to 2008 (Figure 1). The biopsies had been performed from 1969 to 2008 (Table 1). We defined CD as having a SnoMed pathology code equal to VA and did not require a positive CD serology for the diagnosis (see Appendix for a list of Swedish SnoMed codes translated into the international histopathology grading system by Marsh).

**Matched reference individuals**

Records of all patients with CD (n = 29 148), inflammation (n = 13 446) and normal mucosa but positive CD serology (n = 3736) were sent to Statistics Sweden. Each individual with a small intestinal biopsy was then matched with up to five reference individuals (controls) on age, sex, county, and calendar period from the Total Population Register. To protect the integrity of individuals, the PINs of the index individuals and their reference individuals were replaced by serial numbers.

**Exclusions**

We excluded individuals undergoing biopsy where Statistics Sweden had assigned no serial number or controls and where the biopsy may have originated from the ileum (Figure 1). We also excluded controls that could not be matched to an index individual or controls with other data irregularity (Figure 1). These exclusion criteria left us with 46 121 biopsied individuals and 228 632 controls (identical to that of our previous study on mortality). For the purpose of this study, we subsequently excluded individuals with AF before biopsy or study entry (corresponding data in controls), individuals with additional data irregularities and controls where the matched index individual had been excluded for other reasons (since data were analysed by stratum).

The final study sample consisted of 28 637 patients with CD and 141 731 controls with no record of AF before study entry. Secondary reference groups consisted of 12 911 individuals with inflammation and 3673 individuals with normal mucosa but positive CD serology (IgA EMA/transglutaminase: n = 355; IgA gliadin or IgG EMA/transglutaminase/gliadin n = 3318). During most of the follow-up of this study, gliadin was the only available CD antibody in clinical practise (for a detailed description of antibody distribution, we refer to our earlier study).

**Table 1** Characteristics of study participants

<table>
<thead>
<tr>
<th></th>
<th>Matched controls (n = 141 731)</th>
<th>Coeliac disease (n = 28 637)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>88 411 (62.4)</td>
<td>17 821 (62.2)</td>
</tr>
<tr>
<td>Male</td>
<td>53 320 (37.6)</td>
<td>10 816 (37.8)</td>
</tr>
<tr>
<td>Age at study entry, years (median, range)</td>
<td>29; 0–95</td>
<td>30; 0–95</td>
</tr>
<tr>
<td>Attained age, years (median, range)</td>
<td>40; 1–105</td>
<td>40; 1–100</td>
</tr>
<tr>
<td>0–19 (%)</td>
<td>58 847 (41.5)</td>
<td>11 801 (41.2)</td>
</tr>
<tr>
<td>20–39 (%)</td>
<td>26 354 (18.6)</td>
<td>5300 (18.5)</td>
</tr>
<tr>
<td>40–59 (%)</td>
<td>31 996 (22.6)</td>
<td>6435 (22.5)</td>
</tr>
<tr>
<td>≥ 60 (%)</td>
<td>24 534 (17.3)</td>
<td>5101 (17.8)</td>
</tr>
<tr>
<td>Follow-up years (median, range)</td>
<td>9; 0–40</td>
<td>9; 0–40</td>
</tr>
<tr>
<td>Follow-up years (mean ± SD)</td>
<td>10.4 ± 6.4</td>
<td>10.2 ± 6.4</td>
</tr>
<tr>
<td>Calendar year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1989–92</td>
<td>20 212 (14.3)</td>
<td>4085 (14.3)</td>
</tr>
<tr>
<td>1990–99</td>
<td>58 722 (41.4)</td>
<td>11 863 (41.4)</td>
</tr>
<tr>
<td>2000–</td>
<td>62 797 (44.3)</td>
<td>12 689 (44.3)</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>534 (0.4)</td>
<td>922 (3.2)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>799 (0.6)</td>
<td>279 (1.0)</td>
</tr>
<tr>
<td>Autoimmune Thyroid disease</td>
<td>293 (0.2)</td>
<td>193 (0.7)</td>
</tr>
</tbody>
</table>

*Follow-up time until diagnosis of atrial fibrillation, death from other cause, emigration or 31 December 2008. In reference, individuals follow-up can also end through small-intestinal biopsy.
Outcome measure

We defined AF according to relevant ICD (International Classification of Disease) codes in the Swedish National Patient Register (Discharge diagnoses) and the Cause of Death Register (ICD-7 to ICD-10): 433.12; 427.92; 427D, I48. Our definition of AF included inpatients and outpatients, as well as individuals diagnosed with AF as a cause of death. We included primary and secondary diagnoses of AF from the Swedish Patient Register, but only AFs that were listed as the main underlying cause of death. The percentage AF-positive study participants with AF only listed as secondary diagnosis was 10.1% in both groups (CD: n = 97; controls: n = 294).

Covariates

Type 1 diabetes mellitus

We used relevant ICD codes in the National Hospital Discharge Register to identify patients with type 1 diabetes. Until version 9, the Swedish ICD classification did not distinguish between type 1 and type 2 diabetes. In this study, we therefore defined type 1 diabetes as having a hospital discharge diagnosis of diabetes before age 30 years (Table 1). Autoimmune thyroid disease and rheumatoid arthritis were also defined according to relevant ICD codes in Appendix.

Education

When we adjusted for education, we used seven predefined levels, ranging from lower education than 9-year compulsory school to a PhD. This educational information was obtained from the Education Register maintained by Statistics Sweden.

Statistical analysis

Hazard ratios (HRs) for AF were estimated using Cox regression. We used an internally stratified model so that each index individual was only compared with his or her reference individuals within the same stratum (and then a summary risk estimate was calculated). The proportional hazards assumption was examined using log minus log survival curves. Follow-up started on date of first biopsy with VA and the corresponding date in the matched reference individuals.

Follow-up ended with AF diagnosis, emigration, death or on 31 December 2008, whichever event occurred first. In analyses specified a priori, we examined the risk of AF according to follow-up period (<1, 1–4.99, and ≥5 years), age (0–19, 20–39, 40–59, and ≥60 years at first biopsy) and calendar year of first biopsy (1969–1989, 1990–1999, and 2000–2008). We calculated incidence rates as the number of first recorded AF diagnoses divided by person-years until first diagnosis or end of follow-up. In separate analyses, we adjusted for education, country of birth (Nordic country vs. not Nordic country), and for ever having a diagnosis of type 1 diabetes, autoimmune thyroid disease, or rheumatoid arthritis. To increase the specificity of AF, we examined the risk of having an AF diagnosis on at least two separate occasions. In a subanalysis, we also restricted our outcome to having an inpatient diagnosis of AF or death from AF since earlier validation has focused on this subset of patients.

To examine whether the increased risk of AF in CD was specific to CD, we compared the risk of AF in CD patients with that of individuals undergoing small intestinal biopsy but having either inflammation (Marsh 1–2) or normal mucosa (Marsh 0) but positive CD serology.

Post hoc analyses

In a first post hoc analysis, the individual’s age, instead of years of follow-up since biopsy, was used as time-scale in the Cox regression. In a second post hoc analysis, thyroid disease, type 1 diabetes, and rheumatoid arthritis were modelled as time-dependent covariates (Appendix). In a third post hoc analysis, we used logistic regression to examine the relationship between CD and the prevalence of AF (outcome is AF).

In a sample of study participants (individuals with CD: n = 2524; reference individuals: n = 12 137), we had data on smoking and body mass index (BMI) from the Medical Birth Register. The Medical Birth Register started in 1973, but smoking was not recorded until 1983. Smoking data are recorded at the first antenatal visit in approximately gestational week 12 according to three categories specified a priori (number of cigarettes: 0, 1–9/day, and ≥10/day). BMI is based on reported pre-pregnancy weight and height. In women with available smoking and BMI data, we adjusted for these variables in a separate analysis (see appendix).

We also estimated the risk of AF adjusted for the use of antihypertensive medication as a proxy for hypertension. Data on antihypertensive medication (using the following ATC (pharmaceutical) codes C02, C03, C07, and C08) were retrieved from the Swedish Prescribed Drug Register. This analysis was restricted to 25 942 individuals with CD and
129,866 matched controls, all of whom had a follow-up until at least 1 July 2005 when the Prescribed Drug Register started (see Appendix).

It might be hypothesized that small intestinal biopsy could trigger peri-interventional AF. To rule out that the increased risk of AF was due to the mechanical biopsy procedure we excluded all cases of AF in the first week after study entry/biopsy in a separate analysis (see Appendix). Atrial fibrillation may also be precipitated by long-term complications from CD, such as lymphoproliferative malignancy and associated treatments. To rule out that AF was increased as a result of lymphoproliferative malignancy, in a sub-analysis we excluded all patients who ever had a diagnosis of such a malignancy (see Appendix).

Finally, birth weight may influence the risk of both cardiovascular disease and CD. In a subset of individuals with data on birth weight, we adjusted for this variable (12,705 individuals with CD vs. 61,449 reference individuals). Atrial fibrillation in coeliac disease

Coeliac disease and subsequent atrial fibrillation

Coeliac disease was a risk factor for later AF (HR = 1.34; 95% CI = 1.24–1.44) (Table 2). Risk estimates did not change after adjusting for type 1 diabetes, autoimmune thyroid disease, or rheumatoid arthritis (HR = 1.33; 95% CI = 1.23–1.43); nor did the estimate change with adjustment for the level of education (HR = 1.33; 95% CI = 1.22–1.44) or country of birth (HR = 1.34; 95% CI = 1.24–1.44).

Age at diagnosis did not influence the risk of AF (Table 3; P for interaction = 0.324), although patients with childhood CD were younger at end of follow-up (fewer positive events), which resulted in a lower risk estimate for AF with wider CIs. Sex did not influence the risk of AF in patients with CD (Table 3; P for interaction = 0.676).

Patients with CD were at an increased risk of having at least two AF diagnoses (HR = 1.22; 95% CI = 1.11–1.34). When we restricted our outcome to the definition of AF diagnosis used by Smith et al. in their validation of AF in Swedish Registers (Hospital Discharge Register or Cause of Death Register), the HR was 1.32 (95% CI = 1.22–1.43). When the outcome measure was based only on AF in the Swedish Hospital Discharge or Outpatient Registers (and not the Cause of Death Register), the HR was 1.36 (95% CI = 1.26–1.46).

Internal comparison with other individuals undergoing biopsy

Adjusting for age, sex, and calendar year, patients with CD were at a statistically significantly higher risk of AF than patients with normal mucosa but positive CD serology (HR = 1.52; 95% CI = 1.16–1.99) but not compared with individuals with inflammation without VA (HR = 0.97; 95% CI = 0.88–1.08).

Post hoc analysis

Hazard ratios for AF did not change when we modelled thyroid disease, type 1 diabetes, and rheumatoid arthritis as time-dependent covariates (Appendix). The HRs slightly increased when we used age as time-scale instead of the year of follow-up since biopsy (Appendix).

In a post hoc analysis we used logistic regression to examine the relationship between CD and the prevalence of AF (outcome is AF). In such an analysis, an early diagnosis of AF will not influence the risk estimate more than a later diagnosis. In this analysis, patients with CD were at a 1.26-fold increased risk of later AF (95% CI, OR = 1.17–1.36). Adjustment for birth weight did not influence the risk of AF in patients with CD. Data from additional

**Table 2 Risk of atrial fibrillation according to follow-up**

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Observed events</th>
<th>Expected events</th>
<th>HR; 95% CI</th>
<th>Absolute risk/100,000 PYAR (95% CI)</th>
<th>Excess risk/100,000 PYAR (95% CI)</th>
<th>Attributable percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>941</td>
<td>702</td>
<td>1.34; 1.24–1.44</td>
<td>321 (300–341)</td>
<td>81 (71–92)</td>
<td>25</td>
</tr>
<tr>
<td>Year &lt;1</td>
<td>112</td>
<td>56</td>
<td>1.99; 1.61–2.48</td>
<td>396 (323–469)</td>
<td>197 (146–249)</td>
<td>50</td>
</tr>
<tr>
<td>1–4.99</td>
<td>286</td>
<td>217</td>
<td>1.32; 1.16–1.50</td>
<td>283 (250–315)</td>
<td>68 (52–84)</td>
<td>24</td>
</tr>
<tr>
<td>&gt;5</td>
<td>543</td>
<td>431</td>
<td>1.26; 1.14–1.39</td>
<td>332 (304–359)</td>
<td>68 (56–81)</td>
<td>21</td>
</tr>
</tbody>
</table>

Reference is general population comparator cohort. The attributable percentage was calculated as (1 − 1/HR). PYAR, person-years at risk.
post hoc analyses are given in Appendix, and consistently supported a positive association between CD and AF.

**Risk of coeliac disease in patients with atrial fibrillation before coeliac disease diagnosis**

Patients with AF were at increased risk of having a later diagnosis of CD (OR = 1.45; 95% CI = 1.31–1.62).

**Discussion**

In this nationwide population-based study, we found a positive association between CD and AF. The magnitude of the association, however, was relatively small in that CD patients were at ~30% increased risk of having AF diagnosed when compared with the general population. This association was seen both before and after diagnosis and strongest around the time of diagnosis. If this is a causal relationship, then this suggests that immune-mediated disorders (such as CD) might increase the risk of AF.

**Comparison with earlier studies**

A recent study by our group found that CD is a risk factor for cardiovascular disease and that cardiovascular disease is the most common cause of death in CD. In 2004, West et al. reported an increased risk of AF in CD (OR 1.26; 95% CI: 0.97–1.64) that was similar to our findings, even though patients with CD had lower rates of diagnosed hypertension and hypercholesterolaemia. In contrast to the study by West et al., we found a statistically significantly increased risk of AF both before and after CD diagnosis. This finding may partly be due to greater statistical power in the present study.

**Strengths and limitations**

In this nationwide study, we were able to link data on biopsy-verified CD from 28 pathology departments to AF data from two other registers: the Swedish Patient Register and the Cause of Death Register. Earlier validation has shown that 95% of patients (n = 108 of 114) with VA also have CD. Therefore, the positive predictive value of a biopsy with VA for CD (95%) actually exceeds that of a CD diagnosis in the Swedish National Patient Register. In addition, small intestinal biopsy has a very high sensitivity for diagnosed CD. Small intestinal biopsy has been the standard procedure for the diagnosis of CD in Sweden since the 1970s, and 96–100% of all Swedish gastroenterologists and paediatricians report that they perform a biopsy in ≥90% of patients with suspected CD. Further, the AF diagnosis has a very high predictive value (97%) in Swedish registers. Due to the lack of data, we could not examine the subtypes of AF such as paroxysmal, persistent, or persistent AF. A post hoc analysis did however reveal that in CD patients with AF and anticoagulants, gastrointestinal bleedings do not seem to be more frequent than in controls with AF and anticoagulants.

More than 900 patients with CD developed AF during follow-up, giving us unprecedented statistical power to examine the association between the two diseases. Using biopsy data, we were also able to identify individuals undergoing biopsy but without having VA, which allowed us to form secondary reference groups. Internal comparisons between patients with CD and those with normal mucosa but positive CD serology further supported our assumption that macroscopic intestinal inflammation is detrimental to the risk of AF. In this secondary analysis, data on those with normal mucosa but positive CD serology however only originated from half of the Swedish population. It is difficult to judge whether this has had any impact on our results.

This study has some limitations, greatest of which is that part of the risk increase for AF might be due to ascertainment bias, i.e.
around the time of CD diagnosis (or conversely, diagnosis of AF, whichever came first) there is, of necessity, an increased level of health care utilization by the patient. Our finding that the risk of AF was highest in the first year after diagnosis suggests that such a bias is present in our study. However, three facts argue against ascertainment bias as the sole explanation for our findings. First, patients with CD were at a statistically significantly higher risk of AF than were patients having normal mucosa, even though the latter are probably to have undergone additional investigations because of ‘negative biopsy’. Secondly, patients with CD were still at an increased risk of AF more than 5 years after diagnosis. Finally, logistic regression showed an increased risk of AF in patients with biopsy-verified CD.

Another limitation is the lack of data on folic acid and B12 levels. In a subset of individuals with CD, 22% suffered from folic acid deficiency and 14% from B12 deficiency.13

Potential mechanisms

Our findings support a role of autoimmune disease in the pathophysiology of AF, potentially acting through systemic inflammation, which has consistently been linked to AF risk. A major strength of our paper is that we had access to AF data in individuals undergoing biopsy but not having VA. We believe that chronic inflammation may play a role in our findings, given that patients with CD were at a significantly increased risk of AF compared with those with normal mucosa (and positive CD serology), but not when compared with individuals with inflammation but without VA. More profound systemic inflammation (at the time of diagnosis before a gluten-free diet is introduced reducing the inflammation) could be one interpretation of why the HR is so much higher around the time of diagnosis. We also found a positive association before diagnosis of CD when inflammation caused by undiagnosed CD is likely to have been most intense.

Other potential mechanisms explaining the association of CD with AF include confounding by associated diseases, ascertainment bias, nutritional deficiencies, or shared risk factors. We adjusted for the most common associated diseases, type 1 diabetes, rheumatoid arthritis, and thyroid disease, the latter being a well-known risk factor for AF. Whereas CD is associated with low birthweight22 and low BMI,23 AF is associated with high birthweight24 and high BMI.25,26 Hence, confounding by birthweight and BMI are unlikely explanations for our findings. Although we did not have BMI or smoking data in all study participants, the fact that adjustment for these two risk factors in a small subset of women with available data increased rather than decreased the HR for AF suggests that the association between CD and AF is not mediated by BMI or smoking. Using the Prescribed Drug Register, we obtained proxy data for hypertension. Adjustment for hypertension did not alter the HR for AF and hypertension therefore seems unlikely to explain the increased risk of AF in CD. We are not aware of any other risk factors for AF16,27,28 that are also risk factors for CD. Still, we acknowledge that the absence of a rigorous assessment of hypertension and BMI in all study participants constitutes a study limitation.

Although a robust association of elevated inflammatory markers and incident AF has been reported in several studies,4–6,7 the predictive accuracy of such markers is limited4,6 likely representing the aetiological heterogeneity of AF.

Conclusions

In conclusion, AF is more common in patients with CD both before and after CD diagnosis, although the excess risk is small. Potential explanations for the increased risk of AF in CD include shared risk factors and chronic inflammation, but ascertainment bias may also have contributed.

Ethics approval

This project (2006/633–31/4) was approved by the Research Ethics Committee of the Karolinska Institute, Sweden on 14 June 2006.

J.F.L., the Corresponding Author, has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence on a worldwide basis to the European Heart Journal.

J.F.L. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of interest: none declared.

Appendix 1

ICD coding for type 1 diabetes mellitus

Before 1997, the ICD coding for diabetes (ICD-7: 260, ICD-8: 250, ICD-9: 250) did not distinguish between type 1 and type 2 diabetes. We defined individuals with type 1 diabetes as those who were ≤30 years of age at their first hospitalization for diabetes (ICD-7-ICD-10).

ICD coding for type 1 thyroid disease

Autoimmune thyroid disease was defined as follows: ICD-7: 252.00, 252.01, 252.02, 253.10, 253.19, 253.20, 253.29, 254.00, ICD-8: 242.00, 242.09, 244, 245.03, ICD-9: 242A, 242X, 244X,
ICD coding for rheumatoid arthritis

ICD-8: 712.3, 714.93, ICD-9: 714, ICD-10: M05, M06.

Appendix 2

Additional statistical calculations

Time-scale is age

To rule out that the positive association between CD and AF was due to an incorrect date of diagnosis of CD, we estimated the risk of AF using age as the time-scale rather than years of follow-up. Using age in the analysis did not change the HR [1.34; 95% CI = 1.25–1.44].

Using logistic regression and not taking time of follow-up into account

There is a risk that patients with a newly diagnosed CD are under increased supervision by physicians who might then detect AF just by chance. To avoid this risk, we treated our data as a case–control study with prevalence of AF as the outcome (not taking time of follow-up into account). A logistic regression revealed an OR of 1.26 [95% CI = 1.17–1.36].

Time-dependent covariates

Definition of covariates (other autoimmune diseases)

In this paper, we treated the covariates type 1 diabetes, rheumatoid arthritis, and autoimmune thyroid disease as fixed covariates (diabetes: 1 = ever having a diagnosis of diabetes; 0 = never having a record of a diagnosis of diabetes, etc.). In separate analyses, we also estimated the risk of AF when taking date of diagnosis of these covariates into account (time-dependent covariates). These analyses did not change the risk estimates:

- Adjusting for type 1 diabetes: HR = 1.36; 95% CI = 1.28–1.44
- Adjusting for autoimmune thyroid disease: HR = 1.36; 95% CI = 1.28–1.45
- Adjusting for rheumatoid arthritis: HR = 1.37; 95% CI = 1.28–1.46

Anticoagulant treatment after AF and risk of gastrointestinal bleeding

We identified all individuals with a record of anticoagulant medication (ATC code 'B01') in the Swedish Prescribed Drug Register. The Swedish Prescribed Drug Register records outpatient medication since 1 July 2005. Hence, most medication prescribed during the study period (1969–2008) is not covered by this register. We were thereby able to identify 461 individuals with AF who started anti-coagulant treatment after AF (98 with CD and 363 controls). We then used the below ICD codes to identify gastrointestinal bleeding (we restricted our search to ICD10-codes since we were only interested in GI bleedings after the introduction of anticoagulants (starting in 2005)).

- Oesophageal bleeding: K22.8
- K25 to K27 (stomach + small intestine) with the 3rd position ‘0’, ‘1’, ‘2’, ‘4’, ‘5’, and ‘6’
- Acute haemorrhagic gastritis: K29.0
- Bleeding in the anus or rectum: K62.5
- Haematemesis: K92.0
- Melena: K92.1
- Non-specific GI bleeding: K92.2

Three of 98 (3.1%) patients with CD and 5 of 363 (1.4%) controls with AF and later anticoagulant treatment had a later diagnosis of GI bleeding (Fisher’s exact test: $P = 0.375$). This difference was not statistically significant.

Adjusting for body mass index and smoking in a subset of women with earlier pregnancy

Adjusting for pre-pregnancy, BMI and smoking in a subset of women did not change the risk estimate more than marginally (not adjusted for BMI or smoking: HR = 3.69; 95% CI = 1.18–11.56; adjusted HR = 4.14; 95% CI = 1.21–14.20).

Adjusting for antihypertensive medication as a proxy for hypertension

Adjustment for antihypertensive medication, as a proxy for hypertension did not affect HRs more than marginally in individuals with a follow-up until at least 1 July 2005 (unadjusted HR: 1.40; 95% CI = 1.24–1.59 and adjusted HR = 1.36; 95% CI = 1.21–1.58).

Adjusting for periinterventional atrial fibrillation

Hazard ratio for AF in CD excluding AF that potentially occurred within 1 week was 1.34 (95% CI = 1.24–1.44).

Adjusting for lymphoproliferative cancer

We used ICD-codes 200–204 (ICD7 to ICD9) and C82-C85 (ICD10) in our dataset to identify individuals with an inpatient diagnosis of lymphoproliferative cancer. In a separate analysis, we then excluded anyone who at some stage of life had a lymphoproliferative cancer.

Excluding individuals with a life-time history of lymphoproliferative cancer (analysis based on 28 425 individuals with CD and 141 366 controls), the HR for AF was 1.35 (95% CI = 1.25–1.45).

Adjusting for birth weight

When we restricted our analysis to individuals with data on birthweight, the unadjusted HR for AF in patients with CD was 1.22 (95% CI = 0.49–3.01), and after adjustment for birthweight (categories according to table above) it was 1.26 (95% CI = 0.51–3.14).
Appendix 3

Table A Comparison of small intestinal histopathology classifications

<table>
<thead>
<tr>
<th>Classification used in this project</th>
<th>villous atrophy</th>
<th>type Ilia</th>
<th>type Ilb</th>
<th>type Ilic</th>
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<tr>
<td>Marsh classification</td>
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<td>Type I Ib</td>
<td>Type I Ic</td>
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<td>Flat</td>
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<td>Coraza et al.29</td>
<td>Grade B1</td>
<td>Grade B2</td>
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<tr>
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<td>VA</td>
<td>IV, subtotal</td>
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<td>++</td>
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References