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Bidirectional relationship between eating disorders and autoimmune diseases

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Abstract

Background: Immune system dysfunction may be associated with eating disorders, and associations could have implications for detection, risk assessment, and treatment of both autoimmune diseases and eating disorders. However, questions regarding the nature of the relationship between these two disease entities remain. We evaluated the strength of associations for the bidirectional relationships between eating disorders and autoimmune diseases. **Methods:** In this nationwide population-based cohort study, Swedish registers were linked to establish a cohort of more than 2.5 million individuals born in Sweden between January 1, 1979 and December 31, 2005 and followed-up until December 2013. Cox proportional hazard regression models were used to investigate: 1) subsequent risk of eating disorders in individuals with autoimmune diseases; and 2) subsequent risk of autoimmune diseases in individuals with eating disorders. **Results:** We observed a strong, bidirectional relationship between the two classes of illness indicating that diagnosis in one illness class increased the risk of the other. In women, autoimmune disease diagnoses increased subsequent hazard of anorexia nervosa, bulimia nervosa, and other eating disorders. Similarly, anorexia nervosa, bulimia nervosa, and other eating disorders increased subsequent hazard of autoimmune diseases. The gastrointestinal-related autoimmune diseases celiac disease and Crohn's disease showed a bidirectional relationship with anorexia nervosa and other eating disorders. Psoriasis showed a bidirectional relationship with other eating disorders. Prior type 1 diabetes increased risk for anorexia nervosa, bulimia nervosa, and other eating disorders. In men, we did not observe a bidirectional pattern, but prior autoimmune arthritis increased risk for other eating disorders. **Conclusions:** The associations between eating disorders and autoimmune diseases provide additional support for previously reported associations. The bidirectional risk pattern observed in women suggests either a shared mechanism or a third mediating variable contributing to the association of these

illnesses.

Keywords: hazard, risk, immune system, cox regression, anorexia nervosa, bulimia nervosa, autoimmunity

Introduction

Autoimmunity has been implicated in several psychiatric disorders (Eaton et al., 2006; Frick & Pittenger, 2016), including eating disorders (for a summary of studies see Table S1). Moreover, the first genome-wide significant association in anorexia nervosa (AN) was identified (Duncan et al., 2017) in a region previously implicated in autoimmune diseases, including type 1 diabetes (Barrett et al., 2009) and arthritis (Okada et al., 2014).

Eating disorders and autoimmunity are complex traits influenced by numerous genetic variants acting additively in combination with environmental factors to influence phenotypic expression (Yilmaz, Hardaway, & Bulik, 2015). Autoimmunity varies on a continuum, ranging from no clinical consequences to pathogenic autoimmunity causing inflammatory organ infiltration, tissue damage, and overt disease-specific symptomatology. Autoimmune diseases occur in ~7-9% of the population and increase with age (Theofilopoulos, Kono, & Baccala, 2017).

Prior epidemiological and molecular genetic evidence of associations between autoimmune diseases and eating disorders coupled with the extensive Swedish health registers afforded an exploration of bidirectional associations between eating disorders and autoimmune diseases (Table S2). We replicated previous findings in an independent sample and extended prior studies (Raevuori et al., 2014; Wotton, James, & Goldacre, 2016; Zerwas et al., 2017) by examining a cohort of more than 2.5 million individuals. The cohort comprises the largest number of female (n = 26,454) and male eating disorder cases (n = 1,711) providing sufficient statistical power, especially in women, to detect epidemiological associations by amassing twice as many cases as earlier studies (Wotton et al. 2016).

Methods

Study Population and Data Sources

We studied individuals aged 0-35 years born in Sweden between January 1, 1979 and December 31, 2005, excluding those who emigrated or died before age 8, or were from multiparous births, to reduce nesting. Individuals were followed until eating disorder onset, autoimmune disease onset, death, emigration from Sweden, or the end of the follow-up period (December 31, 2013), whichever came first. We linked registers using the national personal identification number (Ludvigsson, Otterblad-Olausson, Pettersson, & Ekbom, 2009). Consistent with prior research (Yao et al., 2016), birth year and sex were from the Total Population Register; migration data were from the Migration Register (Statistics Sweden); causes of death were from the Cause of Death Register (Statistics Sweden); and socioeconomic status (SES) was estimated using highest parental education (i.e., completed year 9 or below; completed year 12; >2 years tertiary) from the Longitudinal Integration Database for Health Insurance and Labour Market Studies (Ludvigsson et al., 2016) when the child was 8 years old. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden.

Eating Disorder Outcomes

Eating disorder diagnoses were from the National Patient Register (NPR), which tracks all inpatient care since 1987 and outpatient care since 2001 (Ludvigsson et al., 2011); Riksät-National Quality Register for Treatment for Eating Disorders (since 1999; Emilsson, Lindahl, Köster, Lambe, & Ludvigsson, 2015); the regional quality assurance system for eating disorders, Stepwise (since 2005; Birgegård, Björck, & Clinton, 2010); and the clinical database for child and adolescent psychiatry in Stockholm, Pastill (since 2001; Lindevall, 2009). NPR discharge diagnoses were from Swedish ICD-9 and from ICD-10 (Smedby, 2006). In Riksät and Stepwise, eating disorder diagnoses were based on *DSM-IV-TR*

(American Psychiatric Association, 2005). Coverage in Riksät and Stepwise has increased over time (Javaras et al., 2015). Pastill eating disorder diagnoses were based on ICD-10 or DSM-IV from Child and Adolescent Mental Health Services in Stockholm County (Lindevall, 2009).

Four eating disorder outcomes were evaluated: 1) AN: 307B (Swedish ICD-9); F50.0 or F50.1 (ICD-10); or DSM-IV AN or atypical AN; 2) Other eating disorders: 307F (Swedish ICD-9); F50.2, F50.3, or F50.9 (ICD-10); or DSM-IV bulimia nervosa (BN), atypical BN, binge-eating disorder (BED), or eating disorder not otherwise specified (EDNOS); 3) Any eating disorder: included all individuals with an AN, BN, and/or other eating disorder diagnosis. Consistent with previous reports (Stice, Marti, & Rohde, 2013), many individuals had both AN and other eating disorders (at different times) and are included as incident cases for both the AN and other eating disorder outcomes. Thus, the number of incident cases of AN and/or other eating disorders is greater than the number of incident cases of any eating disorder, where each individual can be an incident case only once. Analysis of any eating disorder provides information on the overall incidence of eating disorders without inflation due to diagnostic crossover. 4) BN: included all individuals who received a BN diagnosis in the NPR (ICD-10: F50.2, F50.3) since 1997 or in Riksät, Stepwise, or Pastill. Analyses of BN are considered secondary because the years of observation are fewer than for the other diagnostic groups. BED and EDNOS could not be separated because Swedish ICD-9 only included a heterogeneous category (eating disorders other than AN) and F50.8, from ICD-10, was not consistently used to code BED in DSM-IV.

Age of onset reflects first contact with the respective diagnosis in the NPR, Riksät, Stepwise, or Pastill after the 8th birthday. The minimum age of onset for eating disorders was 8 to avoid diagnostic misclassification (e.g., childhood feeding difficulties; N excluded=4,493).

Autoimmune Disease Outcome

Autoimmune disease diagnoses were obtained from the NPR using Swedish ICD revisions 8-9 and ICD-10 diagnoses based on year of diagnosis. We evaluated any autoimmune disease as a group, and by specific categories: celiac disease, Crohn's disease, ulcerative colitis, psoriasis, arthritis, lupus, and type 1 diabetes (Table S2). Age of onset was age at first contact with the respective diagnosis in the NPR with no minimum age of onset.

Statistical Analyses

Data management was conducted with SAS version 9.4 analyses were conducted with STATA version 14. False discovery rate (FDR) corrections were made for each predefined set of hypothesis tests (n=128; Benjamini & Hochberg, 2000).

To optimize our longitudinal data, we performed two sets of Cox proportional hazard regression models estimating the relative hazards of eating disorders following autoimmune disease diagnosis and autoimmune disease risk following eating disorder diagnosis. In the first set, autoimmune disease status (presence/absence) was treated as time-dependent diagnosis and calendar year (1987-1996, 1997-2006, 2007-2013) was adjusted for as a time varying variable; all other variables were considered time-independent. For each analysis, we estimated hazard ratios (HR) for eating disorders in individuals exposed to an autoimmune disease compared to those not exposed. In the second set of analyses, we estimated HRs for autoimmune diseases, comparing individuals exposed to an eating disorder to those not exposed, with eating disorder diagnosis as a time-varying diagnosis variable (i.e., event occurring prior to an outcome). All estimates were adjusted for calendar-time in the parametric part of the Cox model, and for age in the nonparametric part. SES was entered as a covariate into all models. In Cox models, HRs greater than 1 indicate a higher risk of illness, whereas HRs less than 1 indicate a lower risk of illness compared with unaffected individuals. Analyses were applied to males and females separately.

Significantly increased HRs, after FDR correction, for an autoimmune disease after eating disorder diagnosis were investigated for effects of temporal proximity by calculating HR for ≤1 year, >1 year to ≤4 years, and >4 years between first and second diagnosis. Due to possible misdiagnosis of eating disorders before age 8, we did not explore temporal proximity between a prior diagnosis of an autoimmune disease and eating disorder onset. Furthermore, we did not investigate different ages of eating disorder onset as age of onset distributions revealed no evidence of bi- or multimodal patterns justifying such an approach, rendering any age at onset cut-off arbitrary (Figures 1a and 1b).

Results

Our cohort comprised 2,545,611 individuals (51.4% males, 48.6% females) followed over 33,640,644 person-years (range: 1 month to 22 years).

Sample characteristics

Table 1 presents prevalence and age at first diagnosis. Eating disorders occurred more commonly in females (2.0%) than in males (0.1%): 94% of eating disorder cases were female.

The most common autoimmune diseases were celiac disease, type 1 diabetes, and psoriasis. A higher percentage of females than males were diagnosed with an autoimmune disease.

Risk of Eating Disorders Following Autoimmune Disease Diagnosis

Tables S3a and S3b provide the results from the Cox regression models estimating HRs of eating disorders after an autoimmune disease diagnosis in males and females, respectively. We discuss only significant results.

In males, any preceding autoimmune disease was associated with an 82% increased

hazard in other eating disorders, a 78% increased hazard in any eating disorder, and a 56% increased hazard for BN. In females, any preceding autoimmune disease increased the hazard for AN by 59%, for other eating disorders by 71%, for any eating disorder by 62%, and for BN by 57%.

We also evaluated the risk for subsequent eating disorders following diagnosis of celiac disease, Crohn's disease, ulcerative colitis, psoriasis, arthritis, lupus, and type 1 diabetes. In males, diagnosis of arthritis increased the risk for other eating disorders by 357% and any eating disorder by 267%, however, the assumption of proportional hazards was violated (Figure 2a). In females, the risk for subsequent AN was increased after celiac disease (50%), Crohn's disease (89%), and type 1 diabetes (71%). Moreover, celiac disease (47%), Crohn's disease (63%), ulcerative colitis (52%), psoriasis (33%), and type 1 diabetes (153%) increased risk for subsequent other eating disorders. Risk for any eating disorder was increased after diagnosis of celiac disease (45%), Crohn's disease (61%), ulcerative colitis (49%), psoriasis (27%), and type 1 diabetes (119%). Risk for subsequent BN was increased by 222% by an earlier diagnosis of type 1 diabetes (Figure 2c).

Risk of Autoimmune Disease Following an Eating Disorder Diagnosis

Tables S4a and S4b provide the results from the Cox regression models estimating risk for subsequent autoimmune disease following an eating disorder diagnosis in males and females. After correcting for multiple testing, we did not observe an increased risk for autoimmune diseases after eating disorder diagnosis in men. However, females with AN (42%), other eating disorders (58%), any eating disorder (53%), or BN (48%) were at increased risk for later any autoimmune disease.

We evaluated the risk for celiac disease, Crohn's disease, ulcerative colitis, psoriasis, arthritis, lupus, and type 1 diabetes following a diagnosis of each of the eating disorder groups in males and females. Males diagnosed with eating disorders did not show an

increased risk for subsequent autoimmune diseases after correcting for multiple testing (Figure 2b). In females, prior diagnosis of AN (83%), other eating disorders (69%), and any eating disorder (72%) increased risk for celiac disease. Other eating disorders (72%) and any eating disorder diagnosis (63%) showed increased risk for Crohn's disease. A diagnosis of other eating disorders increased the risk for subsequent psoriasis by 38% (Figure 2d).

Temporal Proximity of Risk of Autoimmune Disease Following an Eating Disorder Diagnosis

We explored effects of temporal proximity between eating disorder diagnosis and risk for autoimmune disease in females (Table S5) as only females had significant findings. A prior diagnoses of AN was associated with an increased risk (105%) of being diagnosed with any autoimmune disease within the first year after AN diagnosis and with a 49% increased risk between years 1 and 4. Similarly, risk for celiac disease was increased 217% within the first year and 84% in years 1 to 4 after AN diagnosis. A prior diagnoses of other eating disorders increased the risk of being diagnosed with any autoimmune disease for all three time periods: 216% for 1 year after diagnosis; 47% for 1 to 4 years between diagnoses; and 45% for >4 years. Other eating disorders increased the risk of being diagnosed with celiac disease (165%) and Crohn's disease (188%) within the first year. The increased risk for celiac disease persisted between 1 year and 4 years at 55%. Within the first year, females with any eating disorder were at 114% increased risk of developing any autoimmune disease; 48% increased risk between years 1 and 4; and 32% increased risk >4 years. Any eating disorder increased the risk for celiac disease and Crohn's disease within the first year after diagnoses by 189% and 202%, respectively. The risk of being diagnosed with celiac disease persisted between years 1 and 4 at 58%. BN was associated with a 79% increased risk for any autoimmune disease after 4 years of BN diagnosis.

Discussion

With 2.5 million participants and over 26,000 individuals diagnosed with an eating disorder, to our knowledge, this is the largest prospective register-based study examining the bidirectional associations between autoimmune diseases and eating disorders. We observed positive and strong associations between eating disorders and autoimmune diseases that are on par with reported associations in epidemiological investigations between autoimmune diseases and other psychiatric disorders (Benros et al., 2014; Euesden, Danese, Lewis, & Maughan, 2017). We extended previous observations by investigating a variety of autoimmune diseases previously associated with eating disorders in case reports, clinical samples, and smaller cohort studies (Wotton et al., 2016). Our results replicate bidirectional risk patterns of eating disorders and autoimmune diseases explored in two clinical cohort studies (Raevuori et al., 2014; Wotton et al., 2016) and a Danish national study (Zerwas et al., 2017).

In men, we did not observe any bidirectional patterns. Preceding autoimmune arthritis and type 1 diabetes increased the risk for other eating disorders and preceding autoimmune arthritis increased the risk for any eating disorder. The UK study also observed a significantly increased risk for BN in males with type 1 diabetes based on reports from five cases (Wotton et al., 2016).

In women, AN showed a bidirectional relationship with celiac disease, replicating reported results (Mårild et al., 2017; Wotton et al., 2016). Crohn's disease increased risk for AN (Raevuori et al., 2014; Wotton et al., 2016), but was not bidirectionally associated (Wotton et al., 2016). The gastrointestinal-related autoimmune diseases celiac disease and Crohn's disease showed bidirectional relationships with other eating disorders. The Finnish study (Raevuori et al., 2014) showed increased odds for Crohn's disease and BN, whereas the UK study (Wotton et al., 2016) found an increased risk for celiac disease after BN. Ulcerative

colitis increased risk for other eating disorders. Additionally, psoriasis showed a bidirectional relationship with other eating disorders, replicating findings from the UK study (Wotton et al., 2016) and clinical case reports (Crosta et al., 2014; Ferreira, Abreu, Reis, & Figueiredo, 2016). Type 1 diabetes increased risk for AN, other eating disorders, and BN as previously reported (Raevuori et al., 2014; Wotton et al., 2016); however, Wotton et al. (2016) reported an increased risk for type 1 diabetes after AN and BN which we did not replicate.

The bidirectional nature of some associations suggests either a shared underlying mechanism or a third mediating variable that influences risk for both disease groups. Such shared risk-elevating factors could be genetic, environmental, or a combination of both. Current evidence suggests that dysregulated immune function may be one shared underlying mechanism. Several biological factors influencing immune function are described to be predominant or altered in eating disorders: a female preponderance (Chiaroni-Clarke, Munro, & Ellis, 2016; Klein & Flanagan, 2016; McCarthy, Nugent, & Lenz, 2017), metabolic changes mediated by adipokines such as leptin and adiponectin (Abella et al., 2017), elevated cytokines (M. Solmi et al., 2015), abnormal levels of estrogen (Khan & Ansar Ahmed, 2015; Klump, Culbert, & Sisk, 2017), and lower abundance or diversity of intestinal microbiota (Carr, Kleiman, Bulik, Bulik-Sullivan, & Carroll, 2016; Rooks & Garrett, 2016). These factors potentially influence the relationship between eating disorders and autoimmunity. For example, cortisol levels are dysregulated in eating disorders (Monteleone et al., 1999) possibly due to an altered stress response. Cortisol is often included in the therapeutic regimen for autoimmune diseases (Ilzarbe et al., 2017; Straub & Cutolo, 2016).

Furthermore, Fetissov et al. detected autoantibodies against appetite-regulating peptides, including α-Melanocyte-stimulating hormone and adrenocorticotropic hormone in AN and BN (Fetissov et al., 2002, 2005, 2008). However, the role of autoantibodies in autoimmune diseases is not fully understood. Antibodies may be an epiphenomenon or have a

causal effect facilitating aberrant immune cell function leading to cytotoxicity.

Recent research suggests a genetic overlap between several autoimmune diseases and psychiatric disorders; however, the only study that has included eating disorders revealed no significant genetic associations between AN and autoimmune diseases or traits (Tylee et al., 2017). The increased risk for eating disorders after type 1 diabetes could be metabolically mediated through a dysregulation of insulin homeostasis, administration of mandatory external insulin, and insulin misuse (Bryden et al., 1999; Colton et al., 2015).

Elevated body dissatisfaction has been reported in adolescent females with type 1 diabetes (Araia et al., 2017). Moreover, behaviors necessary for diabetes care such as carbohydrate monitoring, restriction and portion control, blood sugar control, and regular exercise have the potential to transition from healthful to pathological thereby increasing risk for eating disorders (Young-Hyman & Davis, 2010). Yet, considerably more research is necessary in this area as a second study reported reduced dieting, fasting, and caloric restriction in adolescents with type 1 diabetes (Ackard et al., 2008).

Similarly, increased risk of any eating disorder after ulcerative colitis could be due to symptom- and therapy-related behavioral changes as treatment often includes dietary changes and a colectomy with pouches or stoma (Ungaro, Mehandru, Allen, Peyrin-Biroulet, & Colombel, 2017). Patients suffering from inflammatory bowel disease often report eating behavior changes related to their disease, and many perceive food as a risk factor for relapse decreasing their pleasure in eating (Zallot et al., 2013). Similarly, the primary treatment component for celiac disease is a gluten-free diet that could significantly influence patients' health-related quality of life (Almagro, Almagro, Ruiz, González, & Martínez, 2018; McAllister, Williams, & Clarke, 2018). Moreover, the increased risk of being diagnosed with a gastrointestinal-related autoimmune disease within the first year of having been diagnosed with an eating disorder may suggest diagnostic uncertainty due to the overlap in their clinical

presentation complicating the differential diagnosis (Golden & Park, 2017; Tokatly Latzer et al., 2018).

Environmental factors (e.g., diet, dietary behavior, and smoking) also influence the human immune system. Starvation and food restriction (as seen in AN) could reduce inflammation and attenuate symptoms in autoimmune illnesses (Hafström, Ringertz, Gyllenhammar, Palmblad, & Harms-Ringdahl, 1988). For gastrointestinal-associated immune diseases, dietary changes are often prescribed to control pain, diarrhea, and bleeding (Lane, Zisman, & Suskind, 2017). All of these processes may be active, and the inclusion of genetic, biological, and environmental confounders, and a developmental perspective in prospective studies are needed to further clarify the relationships between eating disorders and autoimmune diseases.

Strengths and Limitations

Study strengths include the total-population design and substantially more eating disorder cases than in previous studies (Mårild et al., 2017; Raevuori et al., 2014; Wotton et al., 2016; Zerwas et al., 2017). Prospectively collected data allowed us to explore bidirectional risk and minimized the risk of recall bias since data were routinely collected blind to the hypothesis of this study. The positive predictive value between diagnoses for most chronic diseases in the NPR and medical records is generally 85-95% (Ludvigsson et al., 2011). Additionally, we investigated specific autoimmune diseases, which can inform disease detection, treatment, and management. Our statistical models were corrected for multiple statistical tests unlike previous studies (Raevuori et al., 2014; Wotton et al., 2016) and adjusted for socioeconomic status in line with the British sample (Wotton et al., 2016). In addition, the British cohort (Wotton et al. 2016) and our cohort share common ancestry which renders our findings comparable.

The observed bidirectional relationships in females suggest a potential involvement of the immune system in some eating disorders. However, we cannot rule out misdiagnosis or surveillance bias given symptom overlap of eating disorders, especially with gastrointestinal autoimmune diseases, such as Crohn's diseases, ulcerative colitis, or celiac disease. Furthermore, the associations could be a mediated by behaviors, such as eating behavior or dietary restrictions.

Despite the large sample size and follow-up period, some autoimmune disease risk periods remain outside study timeline (e.g., rheumatoid arthritis age of onset is typically after age 44; Symmons, 2002) and exact ages of disease onset cannot be traced in register data. This may also limit the precision of the observed chronological order of eating disorders and autoimmune diseases. Both illnesses could develop at the same time, but one may be diagnosed with a delay, or, they could be diagnosed in opposite order of their onset. Moreover, although the study covers the peak age of onset for eating disorders (Javaras et al., 2015), individuals remain at risk across the lifespan. A longer follow-up period could alter some of the bidirectional relationships. Additionally, we were unable to evaluate BED because it could not be distinguished from other eating disorders in the NPR.

The relatively small number of male eating disorder cases limited our investigation of sex differences. However, compared with previous studies, the investigation represents the largest number of male eating disorder cases in a population sample. Nevertheless, if male eating disorder patients were less likely to seek professional help, this would lead to undersampling and could affect our observed sex ratio (Solmi, Hotopf, Hatch, Treasure, & Micali, 2016). Given the large overall sample size, small differences in prevalence between the sexes would be statistically significant, but their clinical significance questionable. Furthermore, the assumptions of proportional hazards were violated in some of the associations (Tables S3-S4). Lastly, the Swedish versions of ICD-8 and ICD-9 could not

distinguish between type 1 diabetes and type 2 diabetes; however, as our cohort is young (≤34 years), most individuals with ICD-8 or ICD-9 diabetes are assumed to have type 1 diabetes. Diabetes diagnoses according to ICD-10, the largest proportion in our cohort, are classified into type 1 or type 2.

Conclusions

Results support a bidirectional relationship between eating disorders and autoimmune processes in females. However, this phenomenon was not observed in males in our sample. The findings suggest either a shared mechanism contributing to the associations of eating disorders and autoimmune diseases, such as a dysregulation of the immune system or a shared genetic vulnerability, or a third mediating variable may be operative, for instance, autoimmune disease-related changes of eating behavior, medication effects, or insulin dysregulation leading to disturbances of appetite regulation. Clinically, our results encourage vigilance for the emergence of autoimmune diseases in patients with disordered eating behavior because autoimmune diseases and eating disorders show substantial symptom overlap. As the size of genomic investigations of both eating disorders and autoimmune diseases increases, we will be well positioned to further explore the extent to which shared genetic factors may influence risk for both classes of illness. However, first evidence does not support a genetic overlap between autoimmune traits and anorexia nervosa estimated by genetic correlations derived from molecular genetic methods (Tylee et al., 2017). The finding, however, requires replication and extension to other eating disorder types. Identifying common environmental risk factors or mediating metabolic factors, may facilitate the identification of risk factors or profiles and open up new avenues for precision medicine.

Key Points

- In the largest prospective register-based study to date on eating disorders and autoimmune diseases, we replicated strong bidirectional relationships between eating disorders and various autoimmune diseases.
- The observed positive and strong associations between eating disorders and autoimmune diseases are on par with reported associations in epidemiological investigations between autoimmune diseases and other psychiatric disorders.
- Bidirectional, disorder specific patterns were observed in women, but not in men.
- The bidirectional risk pattern observed in females suggests either a shared underlying mechanism or a third mediating variable contributing to the association of these illnesses.
- Our results encourage vigilance for the emergence of autoimmune diseases in patients with disordered eating behavior.

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Table 1. Number (%) of individuals with each eating disorder and autoimmune disease for the total sample and by sex. Mean (SD) age at first diagnosis for each illness by sex.

	Sample	Sex		Age at first diagnosis (years)	
	Total n (%)	Men n (%)	Women n (%)	Men Mean (SD)	Women Mean (SD)
	2,545,611	1,307,906 (51.4)	1,237,705 (48.6)		
Eating disorders[a]					
Anorexia nervosa	12,227 (0.5)	706 (<0.1)	11,521 (0.9)	16.57 (4.2)	17.91 (4.0)
Other eating disorder	20,906 (0.8)	1,340 (0.1)	19,566 (1.6)	17.35 (5.0)	19.50 (4.4)
Any eating disorder	26,454 (1.0)	1,711 (0.1)	24,743 (2.0)	17.03 (4.9)	18.87 (4.4)
Bulimia nervosa	5,898 (0.2)	129 (<0.1)	5,769 (0.4)	21.80 (4.7)	21.66 (3.9)
Autoimmune diseases					
Any autoimmune disease	111,401 (4.4)	48,796 (3.7)	62,605 (5.1)	14.67 (8.2)	15.76 (8.1)
Celiac disease	19,730 (0.8)	7,274 (0.6)	12,456 (1.0)	10.31 (6.9)	11.83 (7.5)
Crohn's disease	8,786 (0.3)	4,377 (0.3)	4,409 (0.4)	18.60 (6.4)	19.68 (6.3)
Ulcerative colitis	10,809 (0.4)	5,752 (0.4)	5,057 (0.4)	19.81 (6.3)	20.32 (6.4)
Psoriasis	18,782 (0.7)	8,787 (0.7)	9,995 (0.8)	19.14 (7.4)	18.82 (7.0)
Arthritis	6,288 (0.2)	1,869 (0.1)	4,419 (0.4)	13.97 (8.4)	16.38 (8.2)
Lupus	1,107 (<0.1)	186 (<0.1)	921 (<0.1)	17.94 (7.4)	20.63 (6.2)
Type 1 diabetes	19,237 (0.8)	10,608 (0.8)	8,629 (0.7)	13.93 (6.7)	13.19 (6.5)

[a]Eating disorder groups are not mutually exclusive. "Other eating disorder" includes bulimia nervosa and eating disorder not otherwise specified. "Any eating disorder" includes anorexia nervosa, bulimia nervosa, and eating

disorder not otherwise specified. Bulimia nervosa statistics are based on diagnoses made since 1997. Incidence cases regardless of prior diagnoses were assigned to each eating disorder group: individuals were assigned to every matching group.

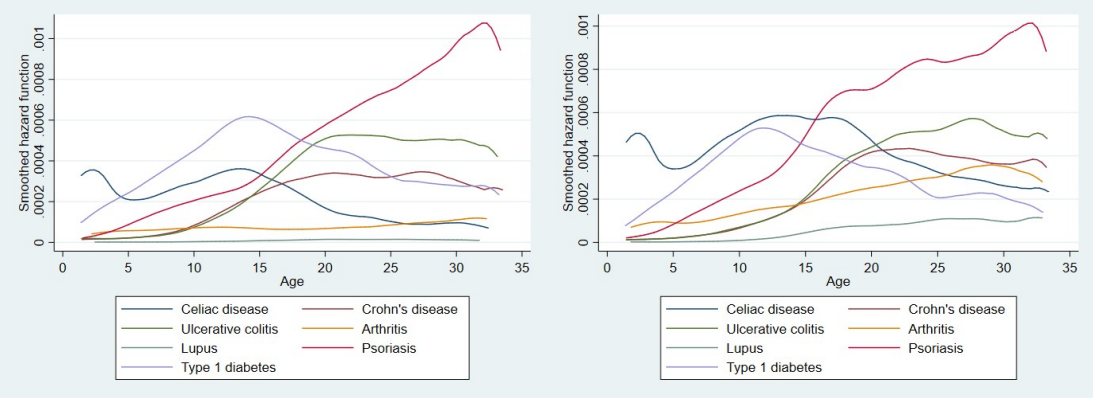
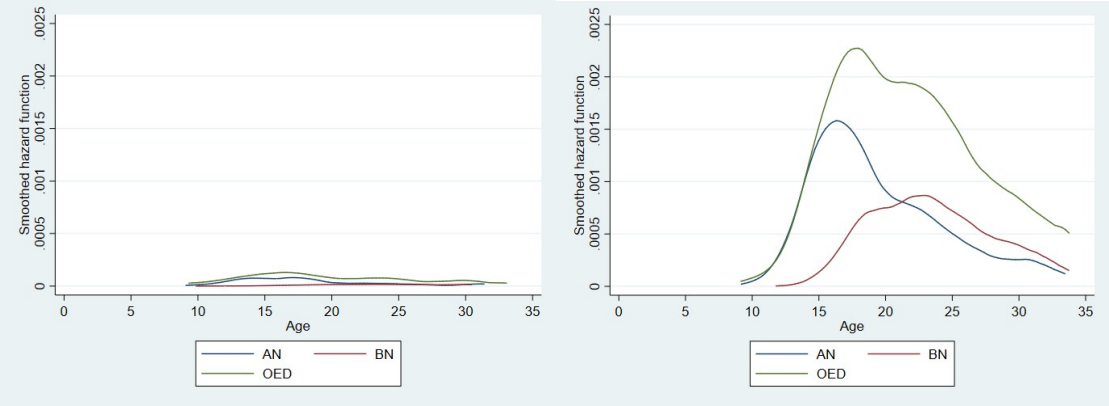


Figure 1a. Hazard by age for each autoimmune disease for men (left) and women (right)



AN =anorexia nervosa, BN = bulimia nervosa, OED = other eating disorder

Figure 1b. Hazard by age for each eating disorder for men (left) and women (right)

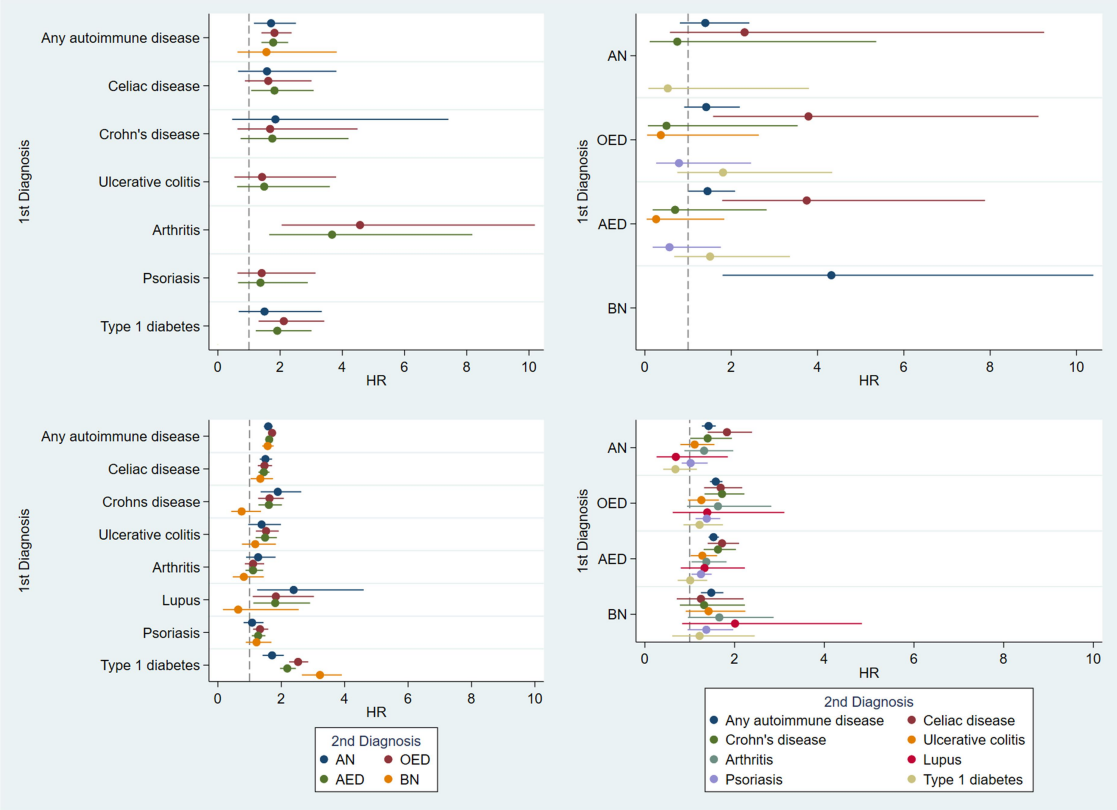


Figure 2a-d. Hazard Ratios (HR) in men 2a-b and women 2c-d. Figures 2a and 2c depict HR for those who develop an eating disorder after autoimmune disease diagnosis. Figures 2b and 2d depict HR for those who develop an autoimmune disease after eating disorder diagnosis. AN =anorexia nervosa, AED = any eating disorder, OED = other eating disorder, BN = bulimia nervosa.

Supporting information:

1. **Table S1.** Table of references of previous association of autoimmune diseases and eating disorders
2. **Table S2.** Autoimmune disease diagnostic codes for Swedish ICD-Revisions 8 and 9 and for ICD-10.
3. **Table S3a.** Hazard ratios evaluating subsequent risk of eating disorders in men with autoimmune diseases.
4. **Table S3b.** Hazard ratios evaluating subsequent risk of eating disorders in women with autoimmune diseases.
5. **Table S4a.** Hazard ratios evaluating subsequent risk of autoimmune diseases in men with eating disorders.
6. **Table S4b.** Hazard ratios evaluating subsequent risk of autoimmune diseases in women with eating disorders.
7. **Table S5.** Temporal proximity between first and second diagnosis.

Table S1. Previous association of autoimmune diseases and eating disorders.

Autoimmune diseases	Description	Anorexia nervosa	Other eating disorders
Celiac disease	Gluten intolerance with mucosa destruction in the small intestine (Kaur, Shimoni, & Wallach, 2017; Lebwohl, Ludvigsson, & Green, 2015)	**Statistical association** Register-based nationwide study (Mårild et al., 2017) Retrospective patient cohort (Wotton, James, & Goldacre, 2016) Cross-sectional study (Karwautz et al., 2008) Retrospective study (Nacinovich et al., 2017) Case reports (Leffler, Dennis, Edwards George, & Kelly, 2007; Ricca et al., 2000; Yucel, Ozbey, Demir, Polat, & Yager, 2006)	**Statistical association** Register-based nationwide study (Butwicka et al., 2017) Retrospective patient cohort (Wotton et al., 2016) Cross-sectional study (Karwautz et al., 2008) Case reports (Jost et al., 2005; Leffler et al., 2007)
		No statistical association Retrospective patient cohort (Raevuori et al., 2014)	**No statistical association** Retrospective patient cohort (Raevuori et al., 2014) Cross-sectional survey (Babio et al., 2018)
Crohn's disease	Chronic inflammatory bowel disease (Torres, Mehandru, Colombel, & Peyrin-Biroulet, 2017)	**Statistical association** Retrospective patient cohort (Raevuori et al., 2014; Wotton et al., 2016) Case reports (Baylé & Bouvard, 2003; Mallett & Murch, 1990; Solmi, Santonastaso, Caccaro, & Favaro, 2013)	**Statistical association** Retrospective patient cohort (Raevuori et al., 2014) Case reports (Meadows & Treasure, 1989)
		No statistical association	**No statistical association** Retrospective patient cohort (Wotton et al., 2016)
Ulcerative colitis	Chronic inflammatory bowel disease (Ananthakrishnan, 2015)	**Statistical association** Retrospective patient cohort (Wotton et al., 2016)	**Statistical association**

		Case reports (Mallett & Murch, 1990; Sreenivasan, 1984)	
		No statistical association Retrospective patient cohort (Raevuori et al., 2014)	**No statistical association** Retrospective patient cohort (Raevuori et al., 2014; Wotton et al., 2016)
Arthritis	Inflammatory disease mainly affecting the joints (Angelotti et al., 2017)	**Statistical association** Retrospective patient cohort (Wotton et al., 2016) Cross-sectional study (Ghadirian, Engelsmann, Leichner, & Marshall, 1993) Case report (Dalbeth & Callan, 2002)	**Statistical association** Retrospective patient cohort (Wotton et al., 2016) Cross-sectional study (Ghadirian et al., 1993)
		No statistical association Retrospective patient cohort (Raevuori et al., 2014)	**No statistical association** Retrospective patient cohort (Raevuori et al., 2014)
Psoriasis	Autoimmune disease with thick, dry, red skin lesions accompanied by pain and itching (Greb et al., 2016)	**Statistical association** Retrospective patient cohort (Wotton et al., 2016)	**Statistical association** Retrospective patient cohort (Wotton et al., 2016) Cross-sectional study (Altunay et al., 2011; Crosta et al., 2014)
		No statistical association Retrospective patient cohort (Raevuori et al., 2014)	**No statistical association** Retrospective patient cohort (Kimball et al., 2012; Raevuori et al., 2014) Patient cohort (Kimball et al., 2012)
Lupus	Systemic autoimmune disease which affects several organs, such as kidneys and skin, can be	**Statistical association** Case reports (Bambery, Malhotra, Kaur, Chadda, & Deodhar, 1987; Sloan, Gallagher,	**Statistical association**

	accompanied by diseases-specific facial erythema and sometimes show psychiatric symptoms (Moulton et al., 2017)	& Walsh, 1998; Toulany, Katzman, Kaufman, Hiraki, & Silverman, 2014)	
		No statistical association Retrospective patient cohort (Raevuori et al., 2014; Wotton et al., 2016)	**No statistical association** Retrospective patient cohort (Raevuori et al., 2014; Wotton et al., 2016)
Type 1 diabetes	Autoimmune disorder affecting the Langerhans' islets of the pancreas leading to subsequent diabetes mellitus (Katsarou et al., 2017)	**Statistical association** Retrospective patient cohort (Raevuori et al., 2014; Scheuing et al., 2014; Takii et al., 2011; Wotton et al., 2016) Survival analysis (Nielsen, Emborg, & Mølbak, 2002) Case report (Brown & Mehler, 2014; Espes, Engström, Reinius, & Carlsson, 2013; Franzese et al., 2002)	**Statistical association** Retrospective patient cohort (Raevuori et al., 2014; Scheuing et al., 2014; Takii et al., 2011; Wotton et al., 2016) Meta-analysis (Mannucci et al., 2005) Case report (Feiereis, 1988; Moosavi, Kreisman, & Hall, 2015)
		No statistical association Meta-analysis (Mannucci et al., 2005) Cohort study (Engström et al., 1999)	**No statistical association** Cohort study (Engström et al., 1999)

The paper by Zerwas et al. investigated a variety of autoimmune diseases but combined them together in two broad categories of autoimmune and autoinflammatory diseases (Zerwas et al., 2017).

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Table S2. Autoimmune disease diagnostic codes for Swedish ICD Revisions 8 and 9 and for ICD-10.

	ICD-8	ICD-9	ICD-10
Autoimmune hepatitis	571.99	571E	K730 K731 K732 K738 K739
Autoimmune thyroiditis	245.00 245.01 245.02 245.03 245.04 245.09	245C	E063
Autoimmune encephalitis		323W	G048
Guillain-Barre syndrome	354.01	357A	G610
Multiple sclerosis	340.99	340	G35
Sjögren's syndrome	734.90	710C	M350
Thyrotoxicosis (Grave's disease)	242.00 242.09 242.10 242.20	242A 242B 242C 242D 242E 242W 242X	E05 E050 E0509 E051 E052 E053 E054 E055 E058 E059
Type 1 diabetes	250.00 250.01 250.02 250.03 250.04 250.05 250.06 250.07 250.08 250.09	250 250A 250AA 250AB 250AK 250B 250BB 250C 250D 250E 250F 250G 250G9 250H 250X 250XB	E10
Crohn's disease (regional enteritis)	563.00	555 555A 555B 555C 555X	K500 K501 K508 K509
Autoimmune hepatitis, chronic active hepatitis	571.90 571.98 571.99	571E	K732

	ICD-8	**ICD-9**	**ICD-10**
Ulcerative colitis	563.10	556	K51 K510 K512 K513 K518 K519
Primary biliary cirrhosis		571G	K743
Celiac disease	269.00	579A	K900
Ankylosing spondylitis	712.40	720A 720B 720C 720W 720X	M45 M081
Dermatopolymyositis	716.00 716.10	710D 710E	M330 M331 M332 M339
Myositis	717.98	728W 729B	M60 M601 M608 M609
Dermatitis herpetiformis	693.99	694A 694C	L122 L130
Arthritis (Still's, juvenile, systematic juvenile, idiopathic, seropositive rheumatoid arthritis, other rheumatoid arthritis)	712.00 712.10 712.20 712.38 712.39 712.50 714.93	714A 714B 714C 714D 714W 714X	M058 M059 M080 M060 M061 M062 M063 M064 M068 M069 M080 M123
Lupus (systemic lupus erythematosus, discoid lupus erythematosus)	734.10 695.40	710A 695E	M321 M328 M329 L930
Mixed connective tissue disease	734.91	279N	M350 M351 M352 M353 M355 M356 M357 M358 M359
Myasthenia gravis	733.00	358A	G700

Primary adrenocortical insufficiency (other adrenal gland)	255.10	255E	E271
	ICD-8	**ICD-9**	**ICD-10**
Pemphigus	694.00 694.01 694.03 694.04 694.09	694E	L100 L101 L102 L103 L104 L108 L109
Pemphigoid	694.02	694F	L120 L121 L122 L123 L128 L129
Polyarteritis nodosa (microscopic polyangiitis)	446.00	446A	M300
Churg-Strauss syndrome (Eosinophilic granulomatosis with polyangiitis)	446.10 446.98	446E 446F 446H	M301
Granulomatosis with polyangiitis (Wegener's granulomatosis)	446.20 446.30 446.38 446.40	446 446A 446E 446F 446G 446H 725	M311 M313 M314 M315 M316 M317
Psoriasis (vulgaris, psoriatic arthritis, generalized familial pustular psoriasis)	696.00 696.10 696.19 696.98	694F 696A 696B	L400 L401 L402 L403 L404 L405 L408 L409
Sarcoidosis	135.97 135.99	135	D860 D861 D862 D863 D868 D869
Scleroderma	734.00 734.01 734.09	710B	M340 M341 M342 M348 M349

Rheumatic fever/rheumatic myocarditis	390.97 390.99 391.97 391.99	390	I010 I012 I018 I019
	ICD-8	**ICD-9**	**ICD-10**
Glomerulonephritis	580.99 581.99 582.00 583.99	581 581A 581B 581C 581D 581W 581X 582 582A 582B 582C 582E 582W 582X 583 583A 583B 583C 583E 583G 583H 583W 583X	N00 N01 N03 N05
Kawasaki disease		446B	M303
Raynaud's syndrome	443.00	443A	I730
Interstitial cystitis	595.04	595B	N301
Schnitzler syndrome (Muckle-Wells syndrome)	708.91	708W	L508

Table S3a. Results, hazard ratios (HR) and 95% confidence intervals (CI) from Cox proportional hazard regression models evaluating subsequent risk of eating disorders in men with autoimmune diseases. All models are adjusted for calendar-time, age, and socioeconomic status. False Discovery Rate corrected p-values (Q) and p-values (P) presented. Due to missing values for some of the second diagnoses the number of individuals with a first diagnosis can slightly vary by second diagnosis.

First Diagnosis	Second Diagnosis	First Dx n	Second Dx n (%)	HR	95% CI	Q	P
Any autoimmune disease	AN	48,409	44 (0.1)	1.71	1.16, 2.51	0.12	0.007
	OED	48,409	83 (0.2)	1.82	1.40, 2.37	<0.001	<0.001
	AED	48,409	108 (0.2)	1.78	1.40, 2.26	<0.001	<0.001
	BN	48,409	10 (<0.1)	1.56	0.63, 3.82	>.99	0.34
Celiac disease	AN	7,247	7 (0.1)	1.58	0.65, 3.81	>.99	0.31
	OED	7,247	15 (0.2)	1.62	0.87, 3.01	>.99	0.13
	AED	7,247	21 (0.3)	1.82	1.07, 3.08	0.40	0.03
	BN	7,247	<4	--	--	--	--
Crohn's disease	AN	4,338	5 (0.1)	1.85	0.46, 7.41	>.99	0.39
	OED	4,338	5 (0.1)	1.68	0.63, 4.49	>.99	0.30
	AED	4,338	9 (0.2)	1.75	0.73, 4.20	>.99	0.21
	BN	4,338	<4	--	--	--	--
Ulcerative colitis	AN	5,671	<4	--	--	--	--
	OED	5,671	5 (0.1)	1.42	0.53, 3.80	>.99	0.48
	AED	5,671	6 (0.1)	1.49	0.62, 3.60	>.99	0.37
	BN	5,671	<4	--	--	--	--

Arthritis	AN	1,859	<4	--	--	--	--
	OED	1,859	7 (0.4)	4.57[a]	2.05, 10.19[a]	0.009 [a]	<0.001 [a]
	AED	1,859	7 (0.4)	3.67[a]	1.65, 8.18[a]	0.05 [a]	0.001 [a]
	BN	1,859	<4	--	--	--	--
Lupus	AN	186	<4	--	--	--	--
	OED	186	<4	--	--	--	--
	AED	186	<4	--	--	--	--
	BN	186	<4	--	--	--	--
Psoriasis	AN	8,676	<4	--	--	--	--
	OED	8,676	9 (0.1)	1.41	0.63, 3.14	>.99	0.40
	AED	8,676	10 (0.1)	1.37	0.65, 2.89	>.99	0.40
	BN	8,676	<4	--	--	--	--
Type 1 diabetes	AN	10,544	8 (0.1)	1.50	0.67, 3.34	>.99	0.33
	OED	10,544	22 (0.2)	2.12	1.31, 3.42	0.05	0.002
	AED	10,544	26 (0.3)	1.91	1.22, 3.01	0.11	0.005
	BN	10,544	<4	--	--	--	--

AN = anorexia nervosa; OED = other eating disorder; AED = any eating disorder; BN = bulimia nervosa - diagnosed since 1997; Dx = diagnosis.
n = number of individuals; % = percent
[a] = The assumption of proportional hazards ratios was violated
-- = Not applicable

Table S3b. Results, hazard ratios (HR) and 95% confidence intervals (CI), from Cox proportional hazard regression models evaluating subsequent risk of eating disorders in females with autoimmune diseases. All models are adjusted for calendar-time, age, and socioeconomic status. False Discovery Rate corrected p-values (Q) and p-values (P) presented. Due to missing values for some of the second diagnoses the number of individuals with a first diagnosis can slightly vary by second diagnosis.

First Diagnosis	Second Diagnosis	First Dx n	Second Dx n (%)	HR	95% CI	Q	P
Any autoimmune disease	AN	61,953	947 (1.5)	1.59	1.45, 1.73	<0.001	<0.001
	OED	61,947	1,712 (2.8)	1.71	1.61, 1.81	<0.001	<0.001
	AED	61,947	2,100 (3.4)	1.62	1.53, 1.72	<0.001	<0.001
	BN	61,950	500 (0.8)	1.57	1.40, 1.76	<0.001	<0.001
Celiac disease	AN	12,382	188 (1.5)	1.50	1.32, 1.71	<0.001	<0.001
	OED	12,379	300 (2.4)	1.47	1.26, 1.71	<0.001	<0.001
	AED	12,379	375 (3.0)	1.45	1.28, 1.63	<0.001	<0.001
	BN	12,381	72 (0.6)	1.34	1.03, 1.74	0.15	0.03
Crohn's disease	AN	4,337	77 (1.8)	1.89	1.35, 2.63	0.002	<0.001
	OED	4,337	134 (3.1)	1.63	1.27, 2.08	0.001	<0.001
	AED	4,337	164 (3.8)	1.61	1.28, 2.02	<0.001	<0.001
	BN	4,337	26 (0.6)	0.75	0.42, 1.36	>.99	0.35
Ulcerative colitis	AN	4,979	67 (1.4)	1.38	0.96, 1.99	0.46	0.08
	OED	4,979	129 (2.6)	1.52	1.20, 1.92	0.004	<0.001
	AED	4,979	162 (3.3)	1.49	1.19, 1.86	0.004	<0.001
	BN	4,979	41 (0.8)	1.18	0.76, 1.83	>.99	0.46

Arthritis	AN	4,374	56 (1.3)	1.27	0.89, 1.82	>.99	0.19
	OED	4,374	94 (2.2)	1.11	0.85, 1.46	>.99	0.45
	AED	4,374	116 (2.7)	1.11	0.87, 1.43	>.99	0.40
	BN	4,374	27 (0.6)	0.82	0.47, 1.45	>.99	0.50
Lupus	AN	921	13 (1.4)	2.39[a]	1.24, 4.60[a]	0.06 [a]	0.009[a]
	OED	921	28 (3.0)	1.83	1.10, 3.03	0.12	0.02
	AED	921	32 (3.5)	1.81	1.12, 2.91	0.09	0.02
	BN	921	7 (0.8)	0.64	0.16, 2.55	>.99	0.52
Psoriasis	AN	9,860	107 (1.1)	1.08	0.81, 1.44	>.99	0.59
	OED	9,859	237 (2.4)	1.33	1.11, 1.59	0.02	0.002
	AED	9,859	278 (2.8)	1.27	1.07, 1.50	0.05	0.007
	BN	9,860	74 (0.8)	1.22	0.88, 1.69	>.99	0.24
Type 1 diabetes	AN	8,568	125 (1.5)	1.71	1.41, 2.08	<0.001	<0.001
	OED	8,566	316 (3.7)	2.53	2.25, 2.85	<0.001	<0.001
	AED	8,566	346 (4.0)	2.19	1.96, 2.46	<0.001	<0.001
	BN	8,566	120 (1.4)	3.22	2.65, 3.91	<0.001	<0.001

AN = anorexia nervosa; OED = other eating disorder; AED = any eating disorder; BN = bulimia nervosa - diagnosed since 1997; Dx = diagnosis.
n = number of individuals; % = percent

Table S4a. Results, hazard ratios (HR) and 95% confidence intervals (CI), from Cox proportional hazard regression models evaluating subsequent risk of autoimmune diseases in men with eating disorders. All models are adjusted for calendar-time, age, and socioeconomic status. False Discovery Rate corrected p-values (Q) and p-values (P) presented. Due to missing values for some of the second diagnoses the number of individuals with a first diagnosis can slightly vary by second diagnosis.

First Diagnosis	Second Diagnosis	First Dx n	Second Dx n (%)	HR	95% CI	Q	P
AN	Any autoimmune disease	696	41 (5.9)	1.40	0.81, 2.42	>.99	0.22
	Celiac disease	699	6 (0.9)	2.31	0.58, 9.25	>.99	0.24
	Crohn's disease	700	5 (0.7)	0.75	0.11, 5.36	>.99	0.78
	Ulcerative colitis	699	<4	--	--	--	--
	Arthritis	699	<4	--	--	--	--
	Lupus	700	<4	--	--	--	--
	Psoriasis	700	<4	--	--	--	--
	Type 1 diabetes	700	8 (1.1)	0.53	0.08, 3.80	>.99	0.53
OED	Any autoimmune disease	1,308	73 (5.6)	1.42	0.91, 2.20	>.99	0.12
	Celiac disease	1,317	13 (1.0)	3.79[a]	1.58, 9.12[a]	0.12[a]	0.003[a]
	Crohn's disease	1,319	5 (0.4)	0.50	0.07, 3.54	>.99	0.49
	Ulcerative colitis	1,318	5 (0.4)	0.37	0.05, 2.64	>.99	0.32
	Arthritis	1,317	5 (0.4)	--	--	--	--
	Lupus	1,319	<4	--	--	--	--
	Psoriasis	1,317	7 (0.5)	0.79	0.26, 2.46	>.99	0.69
	Type 1 diabetes	1,317	20 (1.5)	1.81	0.75, 4.34	>.99	0.19

AED	Any autoimmune disease	1,677	96 (5.7)	1.45	1.01, 2.09	>.99	0.05
	Celiac disease	1,687	18 (1.1)	3.75[a]	1.79, 7.88[a]	0.06[a]	<0.001[a]
	Crohn's disease	1,690	9 (0.5)	0.70	0.18, 2.82	>.99	0.62
	Ulcerative colitis	1,689	6 (0.4)	0.26	0.04, 1.84	>.99	0.18
	Arthritis	1,688	5 (0.3)	--	--	--	--
	Lupus	1,690	<4	--	--	--	--
	Psoriasis	1,688	8 (0.5)	0.57	0.18, 1.76	>.99	0.33
	Type 1 diabetes	1,688	24 (1.4)	1.51	0.68, 3.36	>.99	0.31
BN	Any autoimmune disease	124	10 (8.1)	4.32[a]	1.80, 10.39[a]	0.07	0.001[a]
	Celiac disease	124	<4	--	--	--	--
	Crohn's disease	124	<4	--	--	--	--
	Ulcerative colitis	124	<4	--	--	--	--
	Arthritis	124	<4	--	--	--	--
	Lupus	124	<5	--	--	--	--
	Psoriasis	124	<4	--	--	--	--
	Type 1 diabetes	124	<4	--	--	--	--

AN = anorexia nervosa; OED = other eating disorder; AED = any eating disorder; BN = bulimia nervosa - diagnosed since 1997; Dx = diagnosis.
n = number of individuals; % = percent
[a] = The assumption of proportion hazards ratios was violated
-- = Not applicable

Table S4b. Results, hazard ratios (HR) and 95% confidence intervals (CI), from Cox proportional hazard regression models evaluating subsequent risk of autoimmune diseases in women with eating disorders. All models are adjusted for calendar-time, age, and socioeconomic status. False Discovery Rate corrected p-values (Q) and p-values (P) presented. Due to missing values for some of the second diagnoses the number of individuals with a first diagnosis can slightly vary by second diagnosis.

First Diagnosis	Second Diagnosis	First Dx n	Second Dx n (%)	HR	95% CI	Q	P
AN	Any autoimmune disease	11,287	863 (7.7)	1.42	1.27, 1.58	<0.001	<0.001
	Celiac disease	11,343	159 (1.4)	1.83	1.40, 2.39	<0.001	<0.001
	Crohn's disease	11,370	75 (0.7)	1.40	1.01, 1.94	0.38	0.05
	Ulcerative colitis	11,370	65 (0.6)	1.11	0.79, 1.55	>.99	0.56
	Arthritis	11,366	50 (0.4)	1.32	0.88, 1.97	>.99	0.18
	Lupus	11,372	13 (0.1)	0.69	0.26, 1.85	>.99	0.46
	Psoriasis	11,369	104 (0.9)	1.02	0.82, 1.40	>.99	0.61
	Type 1 diabetes	11,360	113 (1.0)	0.68	0.41, 1.16	0.92	0.16
OED	Any autoimmune disease	19,069	1,565 (8.2)	1.58	1.45, 1.73	<0.001	<0.001
	Celiac disease	19,178	258 (1.4)	1.69	1.32, 2.17	<0.001	<0.001
	Crohn's disease	19,215	129 (0.7)	1.72	1.33, 2.22	<0.001	<0.001
	Ulcerative colitis	19,216	126 (0.7)	1.26	0.96, 1.65	0.63	0.09
	Arthritis	19,213	87 (0.5)	1.63	0.94, 2.82	0.16	0.01
	Lupus	19,220	28 (0.2)	1.39	0.62, 3.11	0.62	0.08
	Psoriasis	19,212	231 (1.2)	1.38	1.13, 1.68	0.02	0.002
	Type 1 diabetes	19,178	274 (1.4)	1.22	0.86, 1.74	>.99	0.27

AED	Any autoimmune disease	24,196	1,915 (7.9)	1.53	1.42, 1.65	<0.001	<0.001
	Celiac disease	24,327	316 (1.3)	1.72	1.40, 2.10	<0.001	<0.001
	Crohn's disease	24,381	159 (0.7)	1.63	1.31, 2.03	<0.001	<0.001
	Ulcerative colitis	24,382	159 (0.7)	1.28	1.02, 1.61	0.27	0.03
	Arthritis	24,376	106 (0.4)	1.37	1.04, 1.82	0.27	0.03
	Lupus	24,386	32 (0.1)	1.33	0.80, 2.23	>.99	0.27
	Psoriasis	24,377	271 (1.1)	1.25	1.04, 1.49	0.16	0.02
	Type 1 diabetes	24,342	302 (1.2)	1.01	0.73, 1.39	>.99	0.96
BN	Any autoimmune disease	5,583	474 (8.5)	1.48	1.25, 1.75	<0.001	<0.001
	Celiac disease	5,602	64 (1.1)	1.25	0.71, 2.20	>.99	0.45
	Crohn's disease	5,610	26 (0.5)	1.32	0.78, 2.23	>.99	0.30
	Ulcerative colitis	5,610	41 (0.7)	1.42	0.91, 2.24	0.76	0.13
	Arthritis	5,610	27 (0.5)	1.66	0.96, 2.87	0.54	0.07
	Lupus	5,610	7 (0.1)	2.01	0.83, 4.84	0.76	0.12
	Psoriasis	5,609	73 (1.3)	1.37	0.95, 1.97	0.63	0.09
	Type 1 diabetes	5,599	109 (0.2)	1.22	0.61, 2.45	>.99	0.57

AN = anorexia nervosa; OED = other eating disorder; AED = any eating disorder; BN = bulimia nervosa - diagnosed since 1997; Dx = diagnosis.
n = number of individuals; % = percent

Table S5. Temporal proximity between first and second diagnosis. Results, hazard ratios (HR) and 95% confidence intervals (CI), from Cox proportional hazard regression models evaluating subsequent risk of autoimmune diseases in women with eating disorders.

First Diagnosis	Second Diagnosis	N Years Between First and Second Diagnosis	First Diagnosis n	Second Diagnosis n (%)	HR	95% CI	Q	P
AN	Any autoimmune disease	≤1	1,384	587 (42.4)	2.05	1.63, 2.58	<0.001	<0.001
		1-4	2,904	134 (4.6)	1.49	1.26, 1.77	<0.001	<0.001
		>4	6,999	142 (2.0)	1.15	0.96, 1.37	0.14	0.12
	Celiac disease	≤1	973	123 (12.6)	3.17	1.99, 5.03	<0.001	<0.001
		1-4	2,945	23 (0.8)	1.84	1.22, 2.78	0.007	0.003
		>4	7,425	13 (0.2)	1.14	0.66, 1.97	0.64	0.64
OED	Any autoimmune disease	≤1	2,924	1,148 (39.3)	2.16	1.77, 2.50	<0.001	<0.001
		1-4	6,058	220 (3.6)	1.47	1.28, 1.69	<0.001	<0.001
		>4	10,087	197 (2.0)	1.45	1.24, 1.68	<0.001	<0.001
	Celiac disease	≤1	2,109	216 (10.2)	2.65	1.76, 4.00	<0.001	<0.001
		1-4	6,222	28 (0.5)	1.55	1.06, 2.26	0.04	0.02
		>4	10,847	14 (0.1)	1.19	0.71, 2.02	0.53	0.51
	Crohn's disease	≤1	1,987	82 (4.1)	2.88	1.81, 4.57	<0.001	<0.001
		1-4	6,304	24 (0.4)	1.41	0.93, 2.14	0.13	0.11
		>4	10,924	23 (0.2)	1.54	1.00, 2.37	0.08	0.05
	Psoriasis	≤1	2,039	142 (7.0)	1.48	0.94, 2.32	0.12	0.09
		1-4	6,275	45 (0.7)	1.32	0.97, 1.80	0.10	0.08
		>4	10,898	44 (0.4)	1.4	1.02, 1.91	0.06	0.04
AED	Any autoimmune disease	≤1	3,385	1,344 (39.7)	2.14	1.84, 2.50	<0.001	<0.001
		1-4	6,934	284 (4.1)	1.48	1.31, 1.67	<0.001	<0.001
		>4	1,3877	287 (2.1)	1.32	1.17, 1.50	<0.001	<0.001
	Celiac disease	≤1	2,424	254 (10.5)	2.89	2.05, 4.07	<0.001	<0.001
		1-4	7,079	39 (0.6)	1.58	1.15, 2.18	0.009	0.005
		>4	14,824	23 (0.2)	1.18	0.78, 1.79	0.45	0.42
	Crohn's disease	≤1	2,288	95 (4.2)	3.02	2.00, 4.55	<0.001	<0.001
		1-4	7,163	29 (0.4)	1.34	0.92, 1.96	0.14	0.13
		>4	14,93	35 (0.2)	1.41	0.99, 2.01	0.09	0.06
BN	Any autoimmune disease	≤1	738	341 (46.2)	1.44	0.98, 2.12	0.09	0.06
		1-4	1,687	62 (3.7)	1.25	0.95, 1.64	0.13	0.11
		>4	3,158	71 (2.3)	1.79	1.39, 2.31	<0.001	<0.001

AN = anorexia nervosa, OED = other eating disorder, AED = any eating disorder, BN = bulimia nervosa - diagnosed since 1997; Dx = diagnosis, n = number of individuals, % = percent. All estimates are adjusted for calendar-time,

age, and socioeconomic status. False Discovery Rate corrected p-values (Q) and p-values (P) presented. Temporal proximity results only for estimates that survived FDR correction in Table 2a-b and Table 3a-c.