

Bidirectional relationship between eating disorders and autoimmune diseases

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Background: Immune system dysfunction may be associated with eating disorders (ED) and could have implications for detection, risk assessment, and treatment of both autoimmune diseases and EDs. 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 EDs and autoimmune diseases. **Methods:** In this nationwide population-based 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: (a) subsequent risk of EDs in individuals with autoimmune diseases; and (b) subsequent risk of autoimmune diseases in individuals with EDs. **Results:** We observed a strong, bidirectional relationship between the two illness classes indicating that diagnosis in one illness class increased the risk of the other. In women, the diagnoses of autoimmune disease increased subsequent hazards of anorexia nervosa (AN), bulimia nervosa (BN), and other eating disorders (OED). Similarly, AN, BN, and OED increased subsequent hazards of autoimmune diseases. Gastrointestinal-related autoimmune diseases such as, celiac disease and Crohn's disease showed a bidirectional relationship with AN and OED. Psoriasis showed a bidirectional relationship with OED. The previous occurrence of type 1 diabetes increased the risk for AN, BN, and OED. In men, we did not observe a bidirectional pattern, but prior autoimmune arthritis increased the risk for OED. **Conclusions:** The interactions between EDs and autoimmune diseases support the 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 (ED) (for a summary see Table S1). Moreover, the first genome-wide significant association in anorexia nervosa (AN) (Duncan et al., 2017) was identified 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 EDs coupled with the extensive Swedish health registers afforded an exploration of bidirectional associations (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 ($n = 24,743$) and male ED 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).

Conflict of interest statement: See Acknowledgments for full disclosures.

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 ED first diagnosis, autoimmune disease first diagnosis, 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, & Ekblom, 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); Riksst-National Quality Register for Treatment for EDs (since 1999; Emilsson, Lindahl, Köster, Lambe, & Ludvigsson, 2015); the regional quality assurance system for EDs, 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 Riksst and Stepwise, ED diagnoses were based on *DSM-IV-TR* (American Psychiatric Association, 2005). Coverage in Riksst and Stepwise has increased over time (Javaras et al., 2015). Pastill ED diagnoses were based on ICD-10 or DSM-IV from Child and Adolescent Mental Health Services in Stockholm County (Lindevall, 2009).

Four ED outcomes were evaluated: (a) AN: 307B (Swedish ICD-9); F50.0 or F50.1 (ICD-10); or DSM-IV AN or atypical AN; (b) Other eating disorders (OED): 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 ED not otherwise specified (EDNOS); (c) Any eating disorder (AED): included all individuals with an AN, BN, and/or OED diagnosis. Consistent with previous reports (Stice, Marti, & Rohde, 2013), many individuals had both AN and OED (at different times) and are included as incident cases for both outcomes. Thus, the number of incident cases of AN and/or OED is greater than the number of incident cases of AED, where each individual can be an incident case only once. Analysis of AED provides information on the overall incidence of EDs without inflation due to diagnostic crossover. (d) BN: included all individuals who received a BN diagnosis in the NPR (ICD-10: F50.2, F50.3) since 1997 or in Riksst, 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 (EDs other than AN) and F50.8, from ICD-10, was not consistently used to code BED.

Age at first diagnosis reflects first contact with the respective diagnosis in the NPR, Riksst, Stepwise, or Pastill after the eighth birthday. The minimum age at first diagnosis for EDs was eight 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 the 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 at first diagnosis was age at first contact with the respective diagnosis in the NPR. There was no minimum age at first diagnosis.

Statistical analyses

Data management was conducted with SAS v9.4 and analyses performed by STATA v14. 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 EDs following autoimmune disease diagnosis and autoimmune disease risk following ED 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 EDs 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 ED to those not exposed, with ED 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 >1 indicate a higher risk, whereas HRs <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 ED 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 EDs before age 8, we did not explore temporal proximity between a prior diagnosis of an autoimmune disease and ED onset. Furthermore, we did not investigate different ages of ED onset as age at first diagnosis distributions revealed no evidence of bi- or multimodal patterns justifying such an approach and rendering any age of first diagnosis cut-off arbitrary (Figure 1A and B).

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. EDs occurred more commonly in females (2.0%) than in males (0.1%): 94% of ED 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.

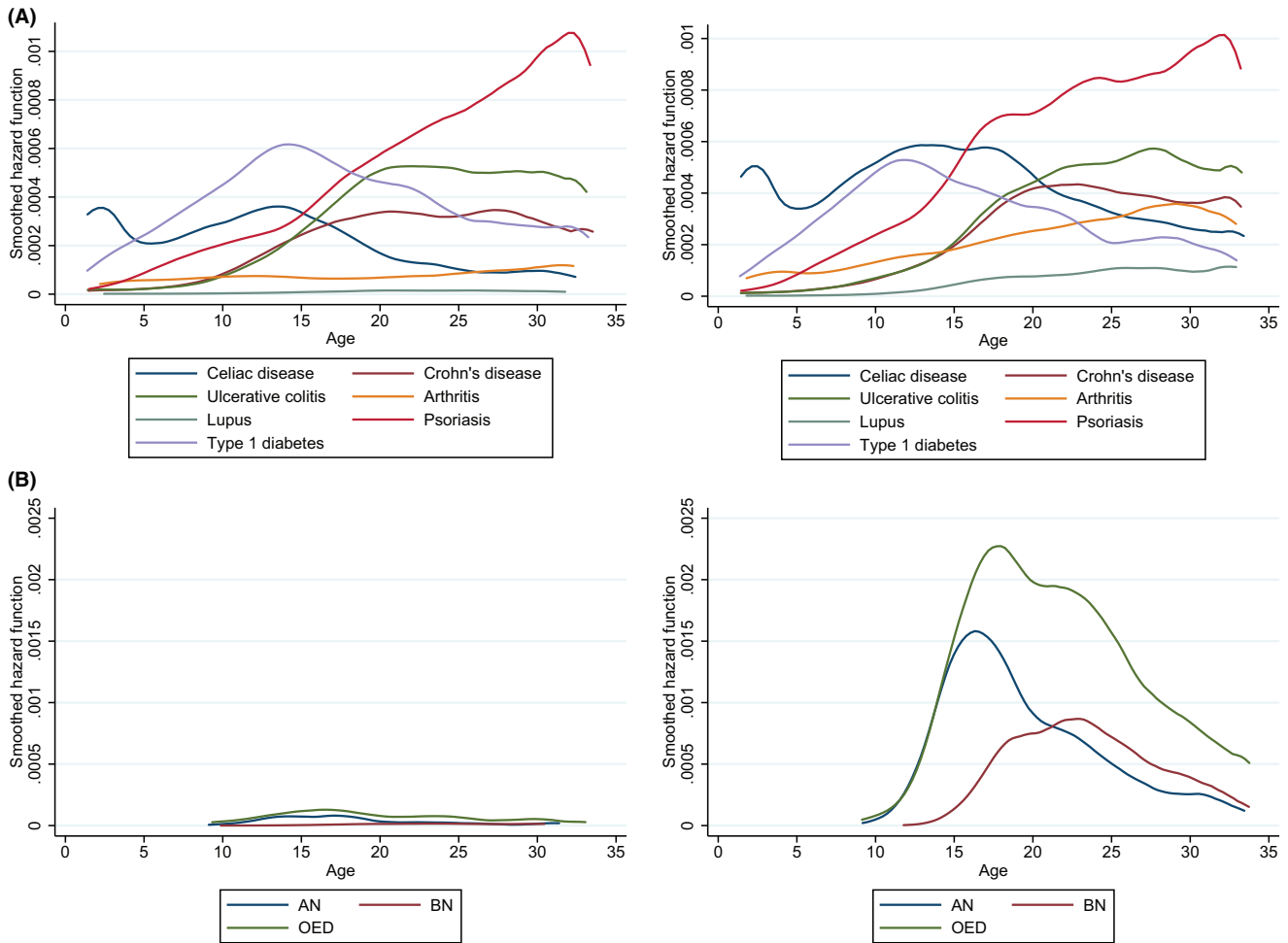


Figure 1 (A) Hazard by age for each autoimmune disease for men (left) and women (right). (B) Hazard by age for each eating disorder for men (left) and women (right). AN, anorexia nervosa; BN, bulimia nervosa; OED, other eating disorder

Risk of eating disorders following autoimmune disease diagnosis

Tables S3a and S3b provide the results from the Cox regression models estimating HRs of EDs 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 OED and a 78% increased hazard in AED. In females, any preceding autoimmune disease increased the hazard for AN by 59%, for OED by 71%, for AED by 62%, and for BN by 57%.

We also evaluated the risk for subsequent ED 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 OED by 357% and AED by 267%, however, the assumption of proportional hazards was violated. A diagnosis of type 1 diabetes also increased risk for OED by 112% (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 OED. Risk for AED 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 ED diagnosis in males and females. After correcting for multiple testing, we did not observe an increased risk for autoimmune diseases after ED diagnosis in men. However, females with AN (42%), OED (58%), AED (53%), or BN (48%) were at increased risk for any later autoimmune disease.

We evaluated the risk for celiac disease, Crohn's disease, ulcerative colitis, psoriasis, arthritis, lupus,

Table 1 Number (%) of individuals with eating disorders and autoimmune diseases for the total sample and by sex

	Sample Total <i>n</i> (%) 2,545,611	Sex		Age at first diagnosis (years)	
		Men <i>n</i> (%) 1,307,906 (51.4)	Women <i>n</i> (%) 1,237,705 (48.6)	Men Mean (SD)	Women Mean (SD)
Eating disorders^a					
Anorexia nervosa (AN)	12,227 (0.5)	706 (<0.1)	11,521 (0.9)	16.57 (4.2)	17.91 (4.0)
Other eating disorder (OED)	20,906 (0.8)	1,340 (0.1)	19,566 (1.6)	17.35 (5.0)	19.50 (4.4)
Any eating disorder (AED)	26,454 (1.0)	1,711 (0.1)	24,743 (2.0)	17.03 (4.9)	18.87 (4.4)
Bulimia nervosa (BN)	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)

^aED groups are not mutually exclusive. 'OED' includes BN and EDNOS. 'AED' includes AN, BN, and EDNOS. BN statistics are based on diagnoses made since 1997. Incident cases regardless of prior diagnoses were assigned to each ED group: individuals were assigned to every matching group.

and type 1 diabetes following a diagnosis of each of the ED groups in males and females. Males diagnosed with EDs did not show an increased risk for subsequent autoimmune diseases after correcting for multiple testing (Figure 2B). In females, prior diagnosis of AN (83%), OED (69%), and AED (72%) increased the risk for celiac disease. OED (72%) and AED diagnosis (63%) showed increased risk for Crohn's disease. A diagnosis of OED 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 ED diagnosis and risk for autoimmune disease in females (Table S5) as only females had significant findings. A prior diagnosis 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 by 217% within the first year and 84% in years 1–4 after AN diagnosis. A prior diagnosis of OED increased the risk of being diagnosed with any autoimmune disease for all three time periods: 116% for 1 year after diagnosis; 47% for 1–4 years between diagnoses; and 45% for >4 years. OED 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 and 4 years at 55%. Within the first year, females with AED were at 114% with increased risk of developing any autoimmune disease; 48% increased risk between years 1 and 4; and 32% increased risk >4 years. AED 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 ED, to our knowledge, this is the largest prospective register-based study examining the bidirectional associations between autoimmune diseases and EDs. We observed positive and strong associations between EDs 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 EDs in case reports, clinical samples, and smaller cohort studies (Table S1). Our results replicate bidirectional risk patterns of EDs 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).

We did not observe any bidirectional patterns in men. Preceding autoimmune arthritis and type 1 diabetes increased the risk for OED and preceding autoimmune arthritis increased the risk for AED. 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

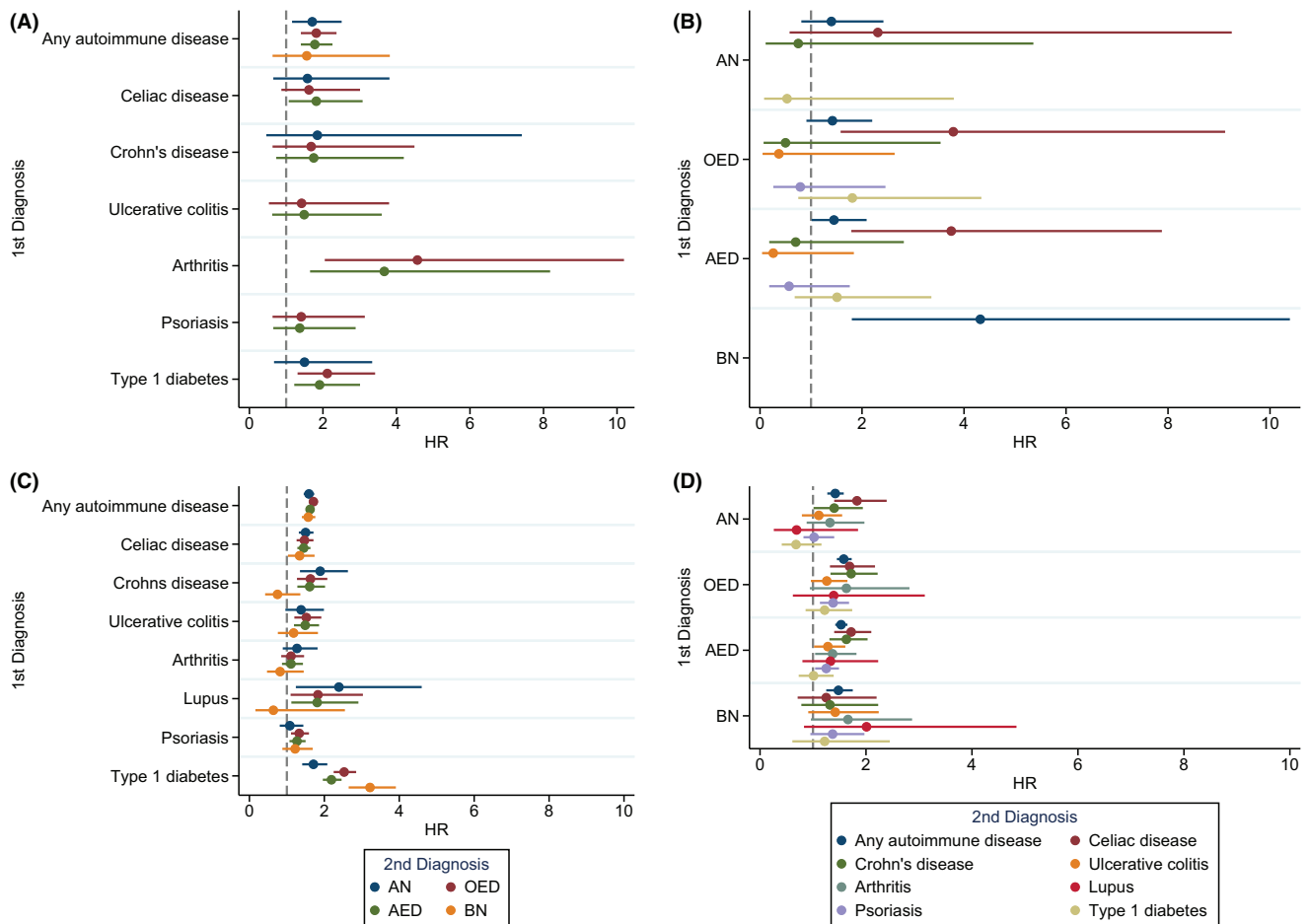


Figure 2 (A–D) Hazard Ratios (HR) in men (A, B) and women (C, D). (A and C) depict HR (95% confidence intervals) for those who develop an eating disorder after autoimmune disease diagnosis. (B and D) depict HR for those who develop an autoimmune disease after eating disorder diagnosis. AN, anorexia nervosa; AED, any eating disorder; OED, other eating disorder; BN, bulimia nervosa

associated (Wotton et al., 2016). The gastrointestinal-related autoimmune diseases such as, celiac disease and Crohn's disease showed bidirectional relationships with OED. 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 OED. Additionally, psoriasis showed a bidirectional relationship with OEDs, 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 the risk for AN, OED, 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 EDs: 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 (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 EDs and autoimmunity. For example, cortisol levels are dysregulated in EDs (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 adrenocorticotrophic 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 EDs revealed no significant genetic associations between AN and autoimmune diseases or traits (Tylee et al., 2017). The increased risk for EDs 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 EDs (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).

In addition, the strict gluten-free diet effective in the treatment of celiac disease could adversely influence patients' health-related quality of life (Almagro, Almagro, Ruiz, González, & Martínez, 2018; McAllister, Williams, & Clarke, 2018), especially for adolescents (Mazzone et al., 2011). The permanent dietary restriction and vigilant monitoring necessary can foster preoccupation with, and anxiety about eating, potentially increasing the risk for pathological eating behaviors (Arigo, Anskis, & Smyth, 2012). Adolescent females with comorbid celiac disease and EDs are more often noncompliant with diet (Wagner et al., 2015), have a higher BMI (Wagner et al., 2015), and have elevated body dissatisfaction (Karwautz et al., 2008). Furthermore, necessary dietary changes can result in weight gain (Colton et al., 2015), which may increase body dissatisfaction and potentially induce restricting and/or purging behaviors (Karwautz et al., 2008).

Likewise, increased risk of AED after ulcerative colitis could reflect symptom- or treatment-related behavioral changes associated with dietary prescriptions and colectomy with pouches or stoma (Ungaro, Mehandru, Allen, Peyrin-Biroulet, & Colombel, 2017). Inflammatory bowel disease patients often report eating behavior changes related to their disease, and many perceive food as a risk factor for relapse thereby decreasing their pleasure in eating (Zallot et al., 2013). Moreover, the increased risk of being diagnosed with gastrointestinal-related autoimmune diseases within the first year of an ED diagnosis may suggest diagnostic uncertainty due to overlap in 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 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 EDs and autoimmune diseases.

Strengths and limitations

Study strengths include the total population design and substantially more ED cases than in previous studies (Mårild et al., 2017; Raevuori et al., 2014; Wotton et al., 2016; Zerwas et al., 2017). Prospectively collected data enabled us to explore bidirectional risk of the classes of illness and minimized recall bias since data were collected blind to study hypotheses. 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 models were corrected for multiple 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). Common ancestry between the British cohort (Wotton et al., 2016) and our Swedish cohort render findings comparable.

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

Despite the large sample size and follow-up period, some autoimmune disease risk periods remain outside the 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 EDs and autoimmune diseases. Both illnesses could develop concurrently, but one may be diagnosed with a delay, or, diagnosed in the opposite order of their onset. Moreover, although the study covers the peak age of onset for EDs (Javaras et al., 2015), with risk persisting across the life span. 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 EDs in the NPR.

Even though this population investigation includes a comparatively large number of male ED cases, we were still limited in ability to demonstrate sex differences. The observed sex ratios in the current study could be affected by ascertainment methodologies (national epidemiological surveys vs. national patient registers). If male ED patients were less likely to seek professional help, then our register-based study would reflect undersampling and a greater sex difference (Solmi, Hotopf, Hatch, Treasure, & Micali, 2016). Indeed, males are more likely to self-report lifetime symptoms on national epidemiological surveys (Hudson, Hiripi, Pope, & Kessler, 2007; Swanson, Crow, Le Grange, Swendsen, & Merikangas, 2011). Combining information from both national registers and participant surveys may aid in the detection of males with EDs (Bulik et al., 2006). Given the large overall sample size, small differences in prevalence between the sexes would be statistically significant, but their clinical significance is questionable. Furthermore, the assumptions of proportional hazards were violated in some of the associations (Tables S3 and S4). Lastly, the Swedish versions of ICD-8 and ICD-9 could not distinguish between type 1 and type 2 diabetes; however, as our cohort is young (≤ 34 years), most individuals with ICD-8 or ICD-9 diabetes are assumed to be type 1. 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 EDs and autoimmune diseases in females. However, this phenomenon was not detected in males. Findings suggest either a shared mechanism, such as a dysregulation of the immune system or a shared genetic vulnerability, or an operative third mediating variable, for instance, autoimmune disease-related changes in 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 EDs show substantial symptom overlap. As the size of genomic investigations of both EDs and autoimmune diseases increases, we will be well positioned to further explore the extent to which shared genetic factors influence risk for both classes of illness. However, first evidence does not support a genetic overlap between autoimmune traits and AN estimated by genetic correlations derived from molecular genetic methods (Tylee et al., 2017). The finding, however, requires replication and extension to other ED 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.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Table S1. Table of references of previous association of autoimmune diseases and eating disorders.

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

Table S3a. Hazard ratios evaluating subsequent risk of eating disorders in men with autoimmune diseases.

Table S3b. Hazard ratios evaluating subsequent risk of eating disorders in women with autoimmune diseases.

Table S4a. Hazard ratios evaluating subsequent risk of autoimmune diseases in men with eating disorders.

Table S4b. Hazard ratios evaluating subsequent risk of autoimmune diseases in women with eating disorders.

Table S5. Temporal proximity between first and second diagnosis.

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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.

References

- Abella, V., Scotece, M., Conde, J., Pino, J., Gonzalez-Gay, M.A., Gómez-Reino, J.J., ... & Gualillo, O. (2017). Leptin in the interplay of inflammation, metabolism and immune system disorders. *Nature Reviews Rheumatology*, *13*, 100–109.
- Ackard, D.M., Vik, N., Neumark-Sztainer, D., Schmitz, K.H., Hannan, P., & Jacobs, D.R., Jr (2008). Disordered eating and body dissatisfaction in adolescents with type 1 diabetes and a population-based comparison sample. *Pediatric Diabetes*, *9*, 312–319.
- Almagro, J.R., Almagro, D.R., Ruiz, C.S., González, J.S., & Martínez, A.H. (2018). The experience of living with a gluten-free diet. *Gastroenterology Nursing*, *41*, 189–200.
- American Psychiatric Association (2005). *Diagnostic and statistical manual of mental disorders* (4th edn, text rev.). Washington, DC: Author.
- Araia, E., Hendrieckx, C., Skinner, T., Pouwer, F., Speight, J., & King, R.M. (2017). Gender differences in disordered eating behaviors and body dissatisfaction among adolescents with type 1 diabetes: Results from diabetes MILES youth-Australia. *International Journal of Eating Disorders*, *50*, 1183–1193.
- Arigo, D., Anskis, A.M., & Smyth, J.M. (2012). Psychiatric comorbidities in women with celiac disease. *Chronic Illness*, *8*, 45–55.
- Barrett, J.C., Clayton, D.G., Concannon, P., Akolkar, B., Cooper, J.D., Erlich, H.A., ... & Type 1 Diabetes Genetics Consortium (2009). Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes. *Nature Genetics*, *41*, 703–707.
- Benjamini, Y., & Hochberg, Y. (2000). On the adaptive control of the false discovery rate in multiple testing with independent statistics. *Journal of Educational and Behavioral Statistics*, *25*, 60–83.
- Benros, M.E., Pedersen, M.G., Rasmussen, H., Eaton, W.W., Nordentoft, M., & Mortensen, P.B. (2014). A nationwide study on the risk of autoimmune diseases in individuals with a personal or a family history of schizophrenia and related psychosis. *American Journal of Psychiatry*, *171*, 218–226.
- Birgegård, A., Björck, C., & Clinton, D. (2010). Quality assurance of specialised treatment of eating disorders using large-scale Internet-based collection systems: Methods, results and lessons learned from designing the Stepwise database. *European Eating Disorders Review*, *18*, 251–259.
- Bryden, K.S., Neil, A., Mayou, R.A., Peveler, R.C., Fairburn, C.G., & Dunger, D.B. (1999). Eating habits, body weight, and insulin misuse. *Diabetes Care*, *22*, 1956–1960.
- Bulik, C.M., Sullivan, P.F., Tozzi, F., Furberg, H., Lichtenstein, P., & Pedersen, N.L. (2006). Prevalence, heritability, and prospective risk factors for anorexia nervosa. *Archives of General Psychiatry*, *63*, 305–312. Erratum in: (2008). *Archives of General Psychiatry*, *65*, 1061.
- Carr, J., Kleiman, S.C., Bulik, C.M., Bulik-Sullivan, E.C., & Carroll, I.M. (2016). Can attention to the intestinal microbiota improve understanding and treatment of anorexia nervosa? *Expert Review of Gastroenterology and Hepatology*, *10*, 565–569.
- Chiaroni-Clarke, R.C., Munro, J.E., & Ellis, J.A. (2016). Sex bias in paediatric autoimmune disease - Not just about sex hormones? *Journal of Autoimmunity*, *69*, 12–23.
- Colton, P.A., Olmsted, M.P., Daneman, D., Farquhar, J.C., Wong, H., Muskat, S., & Rodin, G.M. (2015). Eating disorders in girls and women with type 1 diabetes. *Diabetes Care*, *38*, 1212–1217.
- Crosta, M.L., Caldarola, G., Fraietta, S., Craba, A., Benedetti, C., Coco, V., ... & De Simone, C. (2014). Psychopathology and eating disorders in patients with psoriasis. *Giornale Italiano Di Dermatologia E Venereologia*, *149*, 355–361.
- Duncan, L., Yilmaz, Z., Gaspar, H., Walters, R., Goldstein, J., Anttila, V., ... & Bulik, C.M. (2017). Significant locus and metabolic genetic correlations revealed in genome-wide association study of anorexia nervosa. *American Journal of Psychiatry*, *174*, 850–858.
- Eaton, W.W., Byrne, M., Ewald, H., Mors, O., Chen, C.-Y., Agerbo, E., & Mortensen, P.B. (2006). Association of schizophrenia and autoimmune diseases: Linkage of Danish national registers. *American Journal of Psychiatry*, *163*, 521–528.
- Emilsson, L., Lindahl, B., Köster, M., Lambe, M., & Ludvigsson, J.F. (2015). Review of 103 Swedish healthcare quality registries. *Journal of Internal Medicine*, *277*, 94–136.
- Euesden, J., Danese, A., Lewis, C.M., & Maughan, B. (2017). A bidirectional relationship between depression and the autoimmune disorders - New perspectives from the National Child Development Study. *PLoS ONE*, *12*, e0173015.
- Ferreira, B.I., Abreu, J.L., Reis, J.P., & Figueiredo, A.M. (2016). Psoriasis and associated psychiatric disorders. *Journal of Clinical and Aesthetic Dermatology*, *9*, 36–43.
- Fetissov, S.O., Hallman, J., Oreland, L., af Klinteberg, B., Grenbäck, E., Hulting, A.-L., & Hökfelt, T. (2002). Autoantibodies against α -MSH, ACTH, and LHRH in anorexia and bulimia nervosa patients. *Proceedings of the National Academy of Sciences*, *99*, 17155–17160.
- Fetissov, S.O., Hamze Sinno, M., Coquerel, Q., Do Rego, J.C., Coëffier, M., Gilbert, D., ... & Déchelotte, P. (2008). Emerging role of autoantibodies against appetite-regulating neuropeptides in eating disorders. *Nutrition*, *24*, 854–859.
- Fetissov, S.O., Harro, J., Jaanisk, M., Järv, A., Podar, I., Allik, J., ... & Hökfelt, T. (2005). Autoantibodies against neuropeptides are associated with psychological traits in eating

- disorders. *Proceedings of the National Academy of Sciences of the United States of America*, 102, 14865–14870.
- Frick, L., & Pittenger, C. (2016). Microglial dysregulation in OCD, Tourette Syndrome, and PANDAS. *Journal of Immunology Research*, 2016, 8606057.
- Golden, N.H., & Park, K.T. (2017). Celiac disease and anorexia nervosa—an association well worth considering. *Pediatrics*, 139, e20170545.
- Hafström, I., Ringertz, B., Gyllenhammar, H., Palmblad, J., & Harms-Ringdahl, M. (1988). Effects of fasting on disease activity, neutrophil function, fatty acid composition, and leukotriene biosynthesis in patients with rheumatoid arthritis. *Arthritis and Rheumatism*, 31, 585–592.
- Hudson, J.I., Hiripi, E., Pope, H.G., Jr, & Kessler, R.C. (2007). The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. *Biological Psychiatry*, 61, 348–358.
- Ilzarbe, L., Fàbrega, M., Quintero, R., Bastidas, A., Pintor, L., García-Campayo, J., ... & Ilzarbe, D. (2017). Inflammatory bowel disease and eating disorders. *Journal of Psychosomatic Research*, 102, 47–53.
- Javaras, K.N., Runfola, C.D., Thornton, L.M., Agerbo, E., Birgegård, A., Norring, C., ... & Bulik, C.M. (2015). Sex- and age-specific incidence of healthcare-register-recorded eating disorders in the complete Swedish 1979–2001 birth cohort. *International Journal of Eating Disorders*, 48, 1070–1081.
- Karwautz, A., Wagner, G., Berger, G., Sinnreich, U., Grylli, V., & Huber, W.D. (2008). Eating pathology in adolescents with celiac disease. *Psychosomatics*, 49, 399–406.
- Khan, D., & Ansar Ahmed, S. (2015). The immune system is a natural target for estrogen actions. *Frontiers in Immunology*, 6, 635.
- Klein, S.L., & Flanagan, K.L. (2016). Sex differences in immune responses. *Nature Reviews Immunology*, 16, 626–638.
- Klump, K.L., Culbert, K.M., & Sisk, C.L. (2017). Sex differences in binge eating: Gonadal hormone effects across development. *Annual Review of Clinical Psychology*, 13, 183–207.
- Lane, E.R., Zisman, T.L., & Suskind, D.L. (2017). The microbiota in inflammatory bowel disease. *Journal of Inflammation Research*, 10, 63–73.
- Lindevall, O. (2009). *Pastill—a comprehensive clinical database for child and adolescent psychiatry in Stockholm*. Budapest: European Society for Child and Adolescent Psychiatry.
- Ludvigsson, J.F., Almqvist, C., Bonamy, A.-K.E., Ljung, R., Michaëlsson, K., Neovius, M., ... & Ye, W. (2016). Registers of the Swedish total population and their use in medical research. *European Journal of Epidemiology*, 31, 125–136.
- Ludvigsson, J.F., Andersson, E., Ekbom, A., Feychting, M., Kim, J.-L., Reuterwall, C., ... & Olausson, P.O. (2011). External review and validation of the Swedish national inpatient register. *BMC Public Health*, 11, 450.
- Ludvigsson, J.F., Otterblad-Olausson, P., Pettersson, B.U., & Ekbom, A. (2009). The Swedish personal identity number: Possibilities and pitfalls in healthcare and medical research. *European Journal of Epidemiology*, 24, 659–667.
- Mårild, K., Størdal, K., Bulik, C.M., Rewers, M., Ekbom, A., Liu, E., & Ludvigsson, J.F. (2017). Celiac disease and anorexia nervosa. *Pediatrics*, 139, e20164367.
- Mazzone, L., Reale, L., Spina, M., Guarnera, M., Lionetti, E., Martorana, S., & Mazzone, D. (2011). Compliant gluten-free children with celiac disease: an evaluation of psychological distress. *BMC Pediatrics*, 11, 46.
- McAllister, B.P., Williams, E., & Clarke, K. (2018). A comprehensive review of celiac disease/gluten-sensitive enteropathies. *Clinical Reviews in Allergy and Immunology*. <https://doi.org/10.1007/s12016-018-8691-2>
- McCarthy, M.M., Nugent, B.M., & Lenz, K.M. (2017). Neuroimmunology and neuroepigenetics in the establishment of sex differences in the brain. *Nature Reviews Neuroscience*, 18, 471–484.
- Monteleone, P., Maes, M., Fabrazzo, M., Tortorella, A., Lin, A., Bosmans, E., ... & Maj, M. (1999). Immunoendocrine findings in patients with eating disorders. *Neuropsychobiology*, 40, 115–120.
- Okada, Y., Wu, D., Trynka, G., Raj, T., Terao, C., Ikari, K., ... & Plenge, R.M. (2014). Genetics of rheumatoid arthritis contributes to biology and drug discovery. *Nature*, 506, 376–381.
- Raeuori, A., Haukka, J., Vaarala, O., Suvisaari, J.M., Gissler, M., Grainger, M., ... & Suokas, J.T. (2014). The increased risk for autoimmune diseases in patients with eating disorders. *PLoS ONE*, 9, e104845.
- Rooks, M.G., & Garrett, W.S. (2016). Gut microbiota, metabolites and host immunity. *Nature Reviews Immunology*, 16, 341–352.
- Smedby, B. (2006). *Health classifications in the Nordic countries: Historic development in a national and international perspective*. Copenhagen, Denmark: Nordisk Medicinalstatistisk Komité.
- Solmi, F., Hotopf, M., Hatch, S.L., Treasure, J., & Micali, N. (2016). Eating disorders in a multi-ethnic inner-city UK sample. *Social Psychiatry and Psychiatric Epidemiology*, 51, 369–381.
- Solmi, M., Veronese, N., Favaro, A., Santonastaso, P., Manzano, E., Sergi, G., & Correll, C.U. (2015). Inflammatory cytokines and anorexia nervosa. *Psychoneuroendocrinology*, 51, 237–252.
- Stice, E., Marti, C.N., & Rohde, P. (2013). Prevalence, incidence, and course of the proposed DSM-5 eating disorder diagnoses in an 8-year prospective community study of young women. *Journal of Abnormal Psychology*, 122, 445–457.
- Straub, R.H., & Cutolo, M. (2016). Glucocorticoids and chronic inflammation. *Rheumatology*, 55(suppl 2), ii6–ii14.
- Swanson, S.A., Crow, S.J., Le Grange, D., Swendsen, J., & Merikangas, K.R. (2011). Prevalence and correlates of eating disorders in adolescents. *Archives of General Psychiatry*, 68, 714–723.
- Symmons, D.P.M. (2002). Epidemiology of rheumatoid arthritis. *Clinical Rheumatology*, 16, 707–722.
- Theofilopoulos, A.N., Kono, D.H., & Baccala, R. (2017). The multiple pathways to autoimmunity. *Nature Immunology*, 18, 716–724.
- Tokatly Latzer, I., Rachmiel, M., Zuckerman Levin, N., Mazar-Aronovitch, K., Landau, Z., Ben-David, R.F., ... & Pinhas-Hamiel, O. (2018). Increased prevalence of disordered eating in the dual diagnosis of type 1 diabetes mellitus and celiac disease. *Pediatric Diabetes*, 19, 749–755.
- Tylee, D.S., Sun, J., Hess, J.L., Tahir, M.A., Sharma, E., Malik, R., ... & Glatt, S.J. (2017 August 13). Genetic correlations among neuro-behavioral and immune-related phenotypes based on genome-wide association data. *bioRxiv*, 070730. <https://doi.org/10.1101/070730>.
- Ungaro, R., Mehandru, S., Allen, P.B., Peyrin-Biroulet, L., & Colombel, J.-F. (2017). Ulcerative colitis. *Lancet*, 389, 1756–1770.
- Wagner, G., Zeiler, M., Berger, G., Huber, W.D., Favaro, A., Santonastaso, P., & Karwautz, A. (2015). Eating disorders in adolescents with celiac disease. *European Eating Disorders Review*, 23, 361–370.
- Wotton, C.J., James, A., & Goldacre, M.J. (2016). Coexistence of eating disorders and autoimmune diseases: Record linkage cohort study, UK. *International Journal of Eating Disorders*, 49, 663–672.
- Yao, S., Kuja-Halkola, R., Thornton, L.M., Runfola, C.D., D’Onofrio, B.M., Almqvist, C., ... & Bulik, C.M. (2016). Familial liability for eating disorders and suicide attempts: Evidence from a population registry in Sweden. *JAMA Psychiatry*, 73, 284–291.
- Yilmaz, Z., Hardaway, J.A., & Bulik, C.M. (2015). Genetics and epigenetics of eating disorders. *Advances in Genomics and Genetics*, 5, 131–150.

Young-Hyman, D.L., & Davis, C.L. (2010). Disordered eating behavior in individuals with diabetes: Importance of context, evaluation, and classification. *Diabetes Care*, *33*, 683–689.

Zallot, C., Quilliot, D., Chevaux, J.-B., Peyrin-Biroulet, C., Guéant-Rodriguez, R.M., Freling, E., . . . & Peyrin-Biroulet, L. (2013). Dietary beliefs and behavior among inflammatory bowel disease patients. *Inflammatory Bowel Diseases*, *19*, 66–72.

Zerwas, S., Larsen, J.T., Petersen, L., Thornton, L.M., Quaranta, M., Koch, S.V., . . . & Bulik, C.M. (2017). Eating disorders, autoimmune, and autoinflammatory disease. *Pediatrics*, *140*, e20162089.

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