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Association of Exposure to Infections in Childhood With Risk of Eating Disorders in Adolescent Girls

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IMPORTANCE Infections are recognized as playing a critical role in the risk of psychiatric disorders and suicidal behavior; however, few studies have evaluated the risk of eating disorders.

OBJECTIVE To evaluate the association of hospitalization for infections and treatment with anti-infective agents with the risk of an eating disorder diagnosis.

DESIGN, SETTING, AND PARTICIPANTS A nationwide, population-based, prospective cohort study of 525 643 girls born from January 1, 1989, to December 31, 2006, and followed up until December 31, 2012, was conducted using individual-level data drawn from Danish longitudinal registers. Data were analyzed from January 15 to June 15, 2018, using survival analysis models and adjusted for age, calendar period, parental educational level, and parental history of psychiatric illness.

EXPOSURES Hospital admission for infections and prescribed anti-infective agents for infections.

MAIN OUTCOMES AND MEASURES The main outcome of interest was diagnosis of an eating disorder (anorexia nervosa, bulimia nervosa, or eating disorder not otherwise specified) in a hospital, outpatient clinic, or emergency department setting. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and accompanying 95% CIs.

RESULTS The study population consisted of 525 643 adolescent girls: 2131 received a diagnosis of anorexia nervosa (median [range] age, 15.2 [8.6-21.3] years), 711 received a diagnosis of bulimia nervosa (median [range] age, 17.9 [13.4-22.7] years), and 1398 received a diagnosis of an eating disorder not otherwise specified (median [range] age, 15.6 [8.6-21.6] years). A total of 525 643 adolescent girls were followed up for 4 601 720.4 person-years until a mean age of 16.2 years (range, 10.5-22.7 years). Severe infections that required hospitalization were associated with an increased risk of a subsequent diagnosis of anorexia nervosa by 22% (HR, 1.22; 95% CI, 1.10-1.35), bulimia nervosa by 35% (HR, 1.35; 95% CI, 1.13-1.60), and eating disorder not otherwise specified by 39% (HR, 1.39; 95% CI, 1.23-1.57) compared with adolescent girls without hospitalizations for infections. Infections treated with anti-infective agents were associated with an increased risk of a subsequent diagnosis of anorexia nervosa by 23% (HR, 1.23; 95% CI, 1.10-1.37), bulimia nervosa by 63% (HR, 1.63; 95% CI, 1.32-2.02), and eating disorder not otherwise specified by 45% (HR, 1.45; 95% CI, 1.25-1.67) compared with adolescent girls without infections treated with anti-infective agents.

CONCLUSIONS AND RELEVANCE The findings suggest that hospital-treated infections and less severe infections treated with anti-infective agents are associated with increased risk of subsequent anorexia nervosa, bulimia nervosa, and eating disorders not otherwise specified and that future studies should investigate whether these associations are causal and identify the exact mechanisms between infections and subsequent inflammatory processes with eating disorders.

+ Supplemental content

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nfections and subsequent inflammatory processes are increasingly recognized as playing critical roles in the development of psychiatric disorders[1-7] and suicidal behavior.[8,9] However, to our knowledge, only 2 longitudinal studies[10,11] have assessed the association between infections and eating disorders. In both studies,[10,11] exposure to infections was associated with an increased risk of subsequent eating disorders. Because of differences in the exposure period (prenatal infections[10] vs infections during adolescence[11]), limited access to the full range of infections,[10,11] and infection severity, conclusions are limited. Recent evidence of an association between immune functioning and eating disorders[12] has encouraged further exploration of the association in large population-based studies. We therefore conducted a population-based cohort study to explore the association of infections in childhood with risk of subsequent eating disorder diagnosis in adolescent girls only because the incidence rate of adolescent boys with eating disorders was too low in the Danish population for these analyses.[13]

Infections that occur in the population range in severity, with more severe and rare infections requiring hospital admission and milder ones being treated with anti-infective agents in the primary care setting. Regardless of severity, infections may affect the central nervous system through inflammatory processes[14,15] and/or by triggering autoimmune responses in vulnerable individuals.[16,17] Animal[18] and human disease models[19,20] have demonstrated that systemic inflammation can reach the central nervous system, mediating loss of appetite and taste aversion, which could precipitate eating disorders in vulnerable individuals. Furthermore, altered inflammatory markers have been observed in patients with anorexia nervosa (AN)[21] and in individuals with obesity with co-occurring binge-eating disorder.[22] Several population-based studies[23-25] have revealed positive associations between eating disorders and autoimmune diseases, with a recent genome-wide association study[12] further highlighting the probable involvement of immune-related genes in the liability of eating disorders.

Using a population-based cohort, we evaluated the association of infections with subsequent eating disorder onset. We specifically explored the extent to which the risk of later eating disorders differed according to infection severity, with infections that required hospital contacts indicating greater severity and outpatient anti-infective medication use indicating milder infections. Our analyses evaluated both dose-response and temporal associations. To our knowledge, this was the first population-based register study on all treated infections in the primary and secondary health care sectors to investigate the subsequent diagnosis of eating disorders.

Methods

Study Population

We conducted a population-based cohort study of the entire female population born in Denmark from January 1, 1989, to December 31, 2006, followed up until December 31, 2012, who were alive and residing in Denmark on their sixth birthday and

> ### Key Points
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> **Question** Is a prior infection that requires hospitalization or treatment with an anti-infective agent in childhood associated with an increased risk of eating disorders in adolescent girls?
>
> **Findings** In a Danish population-based cohort study of 525 643 adolescent girls, a prior infection in childhood was associated with an increased risk of later anorexia nervosa, bulimia nervosa, and eating disorder not otherwise specified.
>
> **Meaning** The findings suggest that prior exposure to infections and treatment with anti-infective agents are associated with the development of eating disorders, supporting an emerging immunologic hypothesis.

registered in the Danish Civil Registration System.[26] A personal identification number is used in all national registers, enabling linkage among the registers. Data analysis was performed from January 15 to June 15, 2018. All personal information from the registers is anonymized when used for research purposes, and the project was approved by the Danish Data Protection Agency and Statistics Denmark, necessitating no informed consent.

Registers

The study population was linked to the Danish Psychiatric Central Research Register,[27] which contains data on all admissions to psychiatric inpatient facilities since 1968. Information on nationwide somatic hospital contacts is available from 1977 onward from the Danish National Patient Register.[28] Outpatient information was included from 1995 onward in both registers. Diagnoses were made according to the *International Classification of Diseases, Eighth Revision (ICD-8)*[29] (up to 1994) and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* (from 1995 onward). Treatment in Danish hospitals is free for all residents, and there are no private psychiatric inpatient facilities in Denmark, ensuring that all psychiatric admissions are represented in the registries. The Danish National Prescription Registry[30] contains detailed information from all Danish pharmacies on each redeemed prescription after January 1, 1995.

Assessment of Exposure

The exposures were hospitalizations attributable to infections and redeemed prescriptions for anti-infective agents. We identified hospitalizations for infections since January 1, 1989, and redeemed prescriptions within the primary care sector for anti-infective agents since January 1, 1995. eTable 1 and eTable 2 in the Supplement include the hospitalizations for infections and anti-infective prescriptions evaluated. Because we expected most individuals to have redeemed prescriptions for anti-infective agents at some time,[31] the reference group was chosen to be those having 0 to 2 prescriptions. Thus, exposure was defined as the first hospital contact for infections in the Danish National Patient Register or the date of the third redeemed prescription.

Assessment of Eating Disorder Outcome

The outcomes of interest were a diagnosis registered in the Danish Psychiatric Central Research Register or the Danish National Patient Register of AN (*ICD-10* codes F50.0 and F50.1), bulimia nervosa (BN) (*ICD-10* codes F50.2 and F50.3), and eating disorder not otherwise specified (EDNOS) (*ICD-10* codes F50.8 and F50.9). Consistent with prior research,[32] the eating disorder diagnoses were not considered to be mutually exclusive (eg, an individual could be diagnosed with AN at one time point and contribute to the incidence rate of AN and be diagnosed with BN at a different time point and contribute to the incidence rate of BN). Onset was defined as the admission date of the first inpatient, outpatient, or emergency contact recorded with the specific eating disorder after the age of 6 years.

Statistical Analysis

Primary Analysis

The primary analysis compared individuals who had at least 1 hospital admission for infection with individuals with no hospital admissions and individuals who had 3 or more anti-infective prescriptions with individuals with 0 to 2 prescriptions on risk of subsequent eating disorder diagnosis. We estimated hazard ratios (HRs) of AN, BN, and EDNOS separately. Infections were registered as time dependent. Thus, individuals with an eating disorder before the first infection were counted as being unexposed in the current analyses. We also investigated possible dose-response associations by evaluating the number of hospital admissions (0, 1, 2, or ≥3) or number of prescriptions for an anti-infective agent (0-2, 3-4, 5-9, or ≥10) and eating disorder risk. We explored temporal associations by evaluating the time since the latest hospitalization (0-3 months, 3-6 months, 6-12 months, 1-2 years, 2-5 years, or ≥5 years) and time since the latest prescription for an anti-infective agent (0-3 months, 3-6 months, 6-12 months, 1-2 years, 2-5 years, or ≥5 years) and eating disorder risk.

The HRs were estimated using Cox proportional hazards regression models, with age as the underlying timescale. All analyses were adjusted for age, calendar periods (1995-2000, 2001-2006, and 2007-2012), parental educational level at birth of the proband, and parental history of any psychiatric illness since 1969 (*ICD-8* codes 290-315 and *ICD-10* codes F00-99). Calendar periods and parental history of psychiatric illness were treated as time-dependent variables, whereas parental educational level was considered as time independent. The proportional hazards assumptions were tested based on Schoenfeld residuals. The Wald test was used to assess linear associations, and the HRs, 95% CIs, and *P* values were based on the Wald statistics. All proportional hazards tests results were greater than 0.05 (ie, no violation of the proportional hazards assumption). A 2-sided *P* < .05 based on the χ^2 test was considered to be statistically significant. All analyses were conducted using Stata statistical analysis, version 13 (StataCorp).[33]

Sensitivity Analysis

Because redeemed prescriptions have been registered since January 1, 1995, we performed analyses among all girls born between January 1, 1995, and December 31, 2006, to have a study population with full information regarding medication exposure since birth. To best understand the association between eating disorders and infections, we performed truncated analyses on the risk of eating disorders for the first 12 months from the last hospital admission for infections or a redeemed anti-infective prescription.

Results

The study population consisted of 525 643 girls born in Denmark from January 1, 1989, to December 31, 2006, and followed up for 4 601 720.4 person-years until a mean age of 16.2 years (range, 8.6-22.7 years). In this cohort, 2131 received a diagnosis of AN (median [range] age, 15.2 [10.5-21.3] years), 711 received a diagnosis of BN (median [range] age, 17.9 [13.4-22.7] years), and 1398 received a diagnosis of EDNOS (median [range] age, 15.6 [8.6-21.6] years) from January 1, 1995, to December 31, 2012. The total follow-up time was 4 665 095.1 person-years for AN, 4 671 699.6 person-years for BN, and 4 468 366.5 person-years for EDNOS. Among the adolescent girls, the incidence rate for AN was 46.0 per 100 000 person-years, 15.2 per 100 000 person-years for BN, and 38.8 per 100 000 person-years for EDNOS. The incidence of eating disorders among adolescent boys is reported for descriptive results only. Among adolescent boys, 193 received a diagnosis of AN, 20 received a diagnosis of BN, and 254 received a diagnosis of EDNOS. The incidence rate among boys with AN was 4.0 per 100 000 person-years, 0.4 per 100 000 person-years for BN, and 5.5 per 100 000 person-years for EDNOS. **Table 1** compares hospital stay for infection and number of anti-infective agents with parental history of psychiatric illness and parental educational level.

Hospitalization for Infections

History of hospitalization for an infection compared with no hospitalization was associated with an increased risk of each eating disorder: 22% increase in AN (HR, 1.22; 95% CI, 1.10-1.35), 35% increase in BN (HR, 1.35; 95% CI, 1.13-1.60), and 39% increase in EDNOS (HR, 1.39; 95% CI, 1.23-1.57) (**Table 2**). The risk of receiving a diagnosis of AN was associated with the temporal proximity of the last infection (**Table 3**), with the risks being highest for an AN diagnosis within the first 3 months after a hospitalization for an infection (HR, 2.72; 95% CI, 1.20-5.13; *P* = .007) (**Figure 1**), and we found a dose-response association (HR, 1.10; 95% CI, 1.04-1.15; *P* < .001) (Table 3 and **Figure 2**). The risk of receiving a diagnosis of BN after hospitalization for an infection was also associated with the temporal proximity since the last infection (Table 3), with the risk being highest for a diagnosis of BN within the first 3 months after a hospitalization for an infection (HR, 3.00; 95% CI, 0.96-6.34; *P* = .11) (Figure 1). A dose-response association was evident between hospitalizations and BN (HR, 1.12; 95% CI, 1.03-1.22; *P* = .006) (Table 3 and Figure 2). The risk of EDNOS was also associated with the temporal proximity of the last infection (Table 3), with the risk being highest for a diagnosis of EDNOS within the first 3 months after a hospitalization for an infection (HR, 3.85; 95% CI, 1.72-6.70; *P* < .001) (Figure 1). The

Table 1. Association of Hospital Stay for Infection and Number of Anti-infective Agents
With Parental History of Psychiatric Illness and Parental Educational Level

	No. (%) of Adolescent Girls			
	Hospitalization for Infections Before 6 y of Age		Anti-infective Agents Before 6 y of Age	
Risk Factor	0	≥1	≤2	≥3
Total	442 274 (84.1)	83 529 (15.9)	200 982 (38.2)	324 821 (61.8)
Maternal psychiatric diagnosis[a]	43 279 (9.8)	11 482 (13.8)	18 731 (9.3)	36 030 (11.1)
Paternal psychiatric diagnosis[a]	32 713 (7.4)	7680 (9.2)	15 208 (7.6)	25 185 (7.8)
Highest parental level of education				
Primary education[a]	63 009 (14.3)	14 113 (16.9)	31 659 (15.8)	45 463 (14.0)
Secondary education	17 158 (3.9)	3266 (3.9)	8273 (4.1)	12 151 (3.7)
Vocational education and training	688 (0.2)	141 (0.2)	158 (0.1)	671 (0.2)
Length of higher education				
Short	167 761 (37.9)	30 363 (36.4)	75 496 (37.6)	122 628 (37.8)
Medium	142 422 (32.2)	25 281 (30.3)	60 563 (30.1)	107 410 (33.0)
Long	51 236 (11.6)	10 365 (12.4)	24 833 (12.4)	36 768 (11.3)

[a] Diagnostic crossover between eating disorders was present.

Table 2. Risks of Eating Disorders Depending on Treated Infections Among the 525 643 Study Participants

Risk Factor	Anorexia Nervosa (n = 2131)		Bulimia Nervosa (n = 711)		Eating Disorder Not Otherwise Specified (n = 1398)	
	Participants, No. (%)	HR (95% CI)[a]	Participants, No. (%)	HR (95% CI)[a]	Participants, No. (%)	HR (95% CI)[a]
No hospitalization for infections	1664 (78.1)	1 [Reference]	533 (75.0)	1 [Reference]	1043 (74.6)	1 [Reference]
Any hospitalization for infections	467 (21.9)	1.22 (1.10-1.35)	178 (25.0)	1.35 (1.13-1.60)	355 (25.4)	1.39 (1.23-1.57)
≤2 Anti-infective prescriptions	446 (20.9)	11 [Reference]	107 (15.0)	1 [Reference]	236 (16.9)	1 [Reference]
≥3 Anti-infective prescriptions	1685 (79.1)	1.23 (1.10-1.37)	604 (85.0)	1.63 (1.32-2.02)	1161 (83.1)	1.45 (1.25-1.67)

Abbreviation: HR, hazard ratio.

[a] The analyses were adjusted for age, calendar period, parental educational level, and parental history of psychiatric illness (International Classification of Diseases, Eighth Revision codes 290-315 and International Statistical Classification of Diseases and Related Health Problems, Tenth Revision codes F00-99).

results regarding EDNOS fit a dose-response association (HR, 1.20; 95% CI, 1.13-1.26; P < .001) (Figure 2 and Table 3). Follow-up analyses with gastrointestinal infections specifically suggest that the risk of a diagnosis of EDNOS may be greatest after a hospital stay for a gastrointestinal infection. History of a hospital stay for a gastrointestinal infection was associated with a 60% increase in EDNOS (HR, 1.60; 95% CI, 1.26-2.03) (eTable 3 in the Supplement). The rates of other site-specific (eg, central nervous system) infections in the current study were too low to provide a valid estimate of risk. History of hospitalization for an infection compared with no hospitalization was associated with an increased risk of each eating disorder after controlling for any previous psychiatric illness before the first eating disorder diagnosis (eTable 7 in the Supplement).

Prescription for Anti-infective Agents

Adolescent girls with 3 or more prescriptions for anti-infective agents had an increased risk of all eating disorders

compared with girls with 2 or fewer prescriptions for anti-infective agents (Table 2), and temporal (Table 3) and dose-response associations (Table 3) were present across all eating disorders. Specifically, infections treated with 3 or more redeemed anti-infective agents were associated with a 23% increase in AN (HR, 1.23; 95% CI, 1.10-1.37), 63% increase in BN (HR, 1.63; 95% CI, 1.32-2.02), and 45% increase in EDNOS (HR, 1.45; 95% CI, 1.25-1.67) (Table 2). The risk of AN (HR, 1.30; 95% CI, 1.04-1.50; P = .02), BN (HR, 1.43; 95% CI, 1.01-2.04; P = .02), and EDNOS (HR, 1.64; 95% CI, 1.36-2.28; P < .001) was the highest within the first 3 months after the last redeemed prescription for an anti-infective agent (Figure 1 and Table 3), and as the number of redeemed prescriptions increased, the risk of AN (HR, 1.02; 95% CI, 1.01-1.03; P < .001), BN (HR, 1.04; 95% CI, 1.02-1.07; P < .001), and EDNOS (HR, 1.04; 95% CI, 1.03-1.05; P < .001) increased (Figure 2 and Table 3). Adolescent girls with 3 or more prescriptions for anti-infective agents compared with 2 or fewer had an increased risk of each eating disorder after controlling for any previous mental disorder

Table 3. Risks of Eating Disorders According to Time Since Last Hospital Contact for Infections or Prescriptions for Anti-infective Agents and Number of Hospital Admissions Among the 525 643 Study Participants

Risk Factor	Anorexia Nervosa (n = 2131)		Bulimia Nervosa (n = 711)		Eating Disorder Not Otherwise Specified (n = 1398)	
	Participants, No. (%)	HR (95% CI)[a]	Participants, No. (%)	HR (95% CI)[a]	Participants, No. (%)	HR (95% CI)[a]
Infections that required hospitalization						
No hospital contacts	1664 (78.1)	1 [Reference]	533 (75.0)	1 [Reference]	1043 (74.6)	1 [Reference]
Time since last hospitalization[b]						
0-3 mo	6 (0.3)	2.72 (1.20-5.13)	4 (0.4)	3.00 (0.96-6.34)	5 (0.4)	3.85 (1.72-6.70)
4-6 mo	8 (0.4)	2.21 (1.10-4.31)	5 (0.7)	2.82 (1.17-5.82)	4 (0.3)	1.14 (0.36-3.54)
7-12 mo	23 (1.1)	2.52 (1.67-2.83)	9 (1.3)	2.01 (1.01-3.81)	13 (0.9)	1.95 (1.13-3.38)
>1 to 2 y	34 (1.6)	1.72 (1.22-2.42)	17 (2.4)	1.76 (1.06-2.92)	32 (2.3)	2.22 (1.56-3.18)
>2 to 5 y	66 (3.1)	1.16 (0.91-1.49)	32 (4.5)	1.28 (0.88-1.84)	56 (4.0)	1.38 (1.06-1.81)
>5 y	330 (15.5)	1.13 (1.00-1.27)	112 (15.8)	1.24 (1.01-1.52)	245 (17.5)	1.29 (1.12-1.49)
Overall P value	NA	.003	NA	.007	NA	.01
No. of prescriptions for anti-infective agents						
0-2	446 (20.9)	1 [Reference]	107 (15.0)	1 [Reference]	236 (16.9)	1 [Reference]
Time since last anti-infective agent[b]						
0-3 mo	107 (5.0)	1.30 (1.04-1.50)	57 (8.0)	1.43 (1.01-2.04)	104 (7.4)	1.64 (1.36-2.28)
4-6 mo	201 (9.4)	1.18 (0.98-1.43)	106 (14.9)	1.39 (1.03-2.01)	150 (10.7)	1.30 (1.03-1.64)
7-12 mo	280 (13.1)	1.25 (1.05-1.49)	121 (17.0)	1.36 (1.02-1.82)	234 (16.7)	1.30 (1.05-1.61)
>1 to 2 y	492 (23.1)	1.11 (0.94-1.29)	191 (26.9)	1.33 (1.01-1.75)	333 (23.8)	1.11 (0.91-1.35)
>2 to 5 y	461 (21.6)	0.96 (0.81-1.13)	92 (12.9)	0.86 (0.56-1.08)	259 (18.5)	0.92 (0.75-1.14)
>5 y	144 (6.8)	0.96 (0.78-1.19)	27 (3.8)	0.55 (0.33-0.75)	82 (5.9)	0.80 (0.60-1.06)
Overall P value	NA	<.001	NA	.01	NA	<.001
No. of hospital contacts for infections						
0	1664 (78.1)	1 [Reference]	533 (75.0)	1 [Reference]	1043 (74.6)	1 [Reference]
1	359 (16.9)	1.24 (1.11-1.39)	136 (19.1)	1.36 (1.12-1.64)	252 (18.0)	1.32 (1.14-1.52)
2	73 (3.4)	1.09 (0.86-1.38)	33 (4.6)	1.42 (1.00-2.02)	69 (4.9)	1.52 (1.18-1.94)
≥3	35 (1.6)	1.26 (0.90-1.76)	9 (1.3)	1.00 (0.51-1.93)	34 (2.4)	1.82 (1.29-2.56)
Test for trend P value	NA	.17	NA	.006	NA	<.001
No. of prescriptions for anti-infective agents						
0-2	446 (20.9)	1 [Reference]	107 (15.0)	1 [Reference]	236 (16.9)	1 [Reference]
3-4	357 (16.8)	1.17 (1.01-1.34)	129 (18.1)	1.60 (1.12-1.96)	217 (15.5)	1.30 (1.08-1.56)
5-9	618 (29.0)	1.19 (1.05-1.35)	208 (29.3)	1.48 (1.08-1.79)	427 (30.5)	1.46 (1.24-1.71)
≥10	710 (33.3)	1.33 (1.17-1.51)	267 (37.6)	1.83 (1.34-2.21)	518 (37.1)	1.68 (1.43-1.98)
Test for trend P value	NA	<.001	NA	<.001	NA	<.001

Abbreviations: HR, hazard ratio; NA, not applicable.

[a] The analyses were adjusted for age, calendar period, parental educational level, and parental history of psychiatric illness (*International Classification of Diseases, Eighth Revision* codes 290-315 and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes F00-99).

[b] Time frames represent amount of time after index hospitalization or anti-infective treatment.

before the first eating disorder diagnosis (eTable 8 in the Supplement).

Sensitivity Analyses

Sensitivity analyses were performed among all girls born between January 1, 1995, and December 31, 2006, yielding a subpopulation of 368 118 adolescent girls to restrict analyses to a sample with complete information on hospitalizations for infections and prescriptions for anti-infective agents since birth. Of these adolescent girls, 793 received a diagnosis of AN, 113 received a diagnosis of BN, and 503 received a diagnosis of EDNOS. Hospitalizations for infections were associated with a significant increased risk of BN (HR, 2.00; 95% CI, 1.37-2.92) and EDNOS (HR, 1.44; 95% CI, 1.19-1.75) (eTable 4 in the Supplement). The risk of EDNOS increased as the number of hospitalizations increased (eTable 7 and eTable 8 in the Supplement). Anorexia nervosa, BN, and EDNOS were associated with the temporal proximity of the last hospitalization (eTable 6 in the Supplement), with the risk being highest when the last hospitalization for infections was within the 3 months before the eating disorder diagnosis.

Figure 1. Hazard Ratios for Eating Disorders According to Time Since Last Hospitalization and Last Anti-infective Agent Prescription
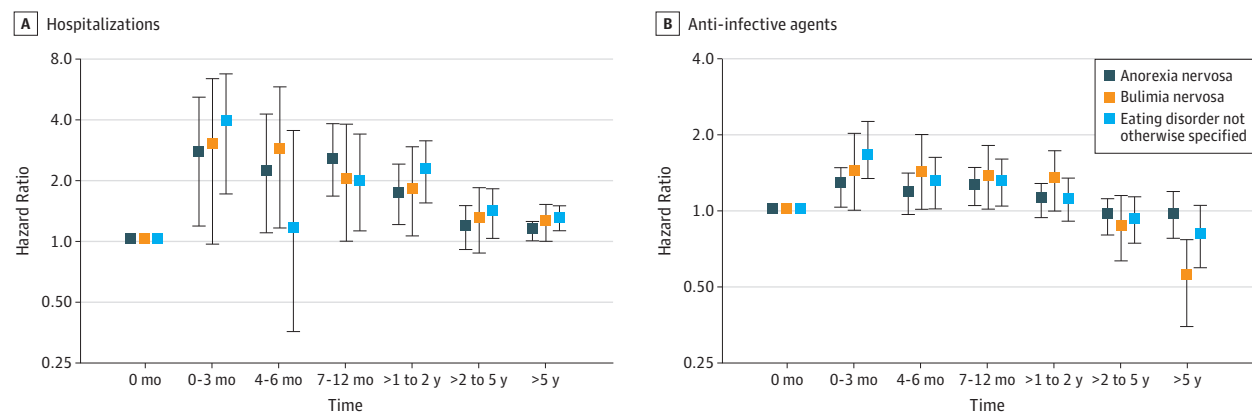
All analyses were adjusted for age, sex, calendar period, parental educational level, and parental history of any psychiatric illness. Error bars indicate 95% CIs.

Figure 2. Hazard Ratios for Eating Disorders According to Number of Hospitalizations and Anti-infective Agent Prescriptions
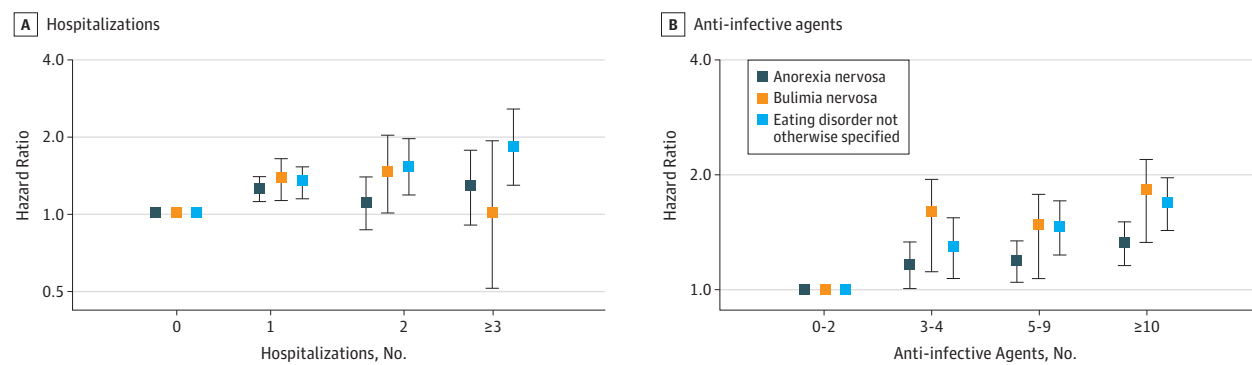
All analyses were adjusted for age, sex, calendar period, parental educational level, and parental history of any psychiatric illness. Error bars indicate 95% CIs.

No significant increased risks of AN (HR, 1.17; 95% CI, 0.96-1.44), BN (HR, 1.47; 95% CI, 0.79-2.75), and EDNOS (HR, 1.08; 95% CI, 0.84-1.39) (eTable 4 in the Supplement) were observed in girls with 3 or more prescriptions for anti-infective agents compared with those with 2 or fewer prescriptions. The risks of BN and EDNOS were highest in the first 3 months of redeeming a prescription for anti-infective agents (eTable 7 and eTable 8 in the Supplement). No dose-response associations were observed.

To address reverse causality, we performed truncated analyses for the risk of eating disorders 12 months from the last hospitalization for an infection or redeemed prescription. The truncated analyses reduced the total follow-up risk time by approximately 1.3 million person-years for individuals with prescriptions (range, approximately 3.2 million to 3.3 million person-years) and by approximately 5000 person-years (range, approximately 4.4 million to 4.6 million person-years) for infections treated in the hospital. Hospitalizations for infections were associated with a significant increased risk of AN (HR, 1.20; 95% CI, 1.08-1.33), BN (HR, 1.33; 95% CI, 1.12-1.57), and EDNOS (HR, 1.40; 95% CI, 1.26-1.56) (eTable 5 in the Supplement). Adolescent girls with 3 or more prescriptions for

anti-infective agents had a significantly greater risk of AN (HR, 1.19; 95% CI, 1.05-1.34), BN (HR, 1.58; 95% CI, 1.23-2.01), and EDNOS (HR, 1.34; 95% CI, 1.16-1.55) compared with those with 2 or fewer prescribed anti-infective agents (eTable 5 in the Supplement).

Discussion

In a population of more than a half million adolescent girls, more than 4000 of whom were diagnosed with an eating disorder, we observed significant associations between infections in childhood and later eating disorder onset. Infections that required hospitalization and 3 or more recorded infections treated with anti-infective agents were associated with an increased risk of AN, BN, and EDNOS. Furthermore, temporal and dose-response associations were observed. Eating disorder onset was associated with time since the last hospitalization or prescription. The risk of AN, BN, and EDNOS onset was greatest in the first 3 months after a hospitalization for an infection. Similarly, the first 3 months after the last redeemed anti-infective agent was the highest-risk period for AN,

BN, and EDNOS onset. Regarding dose response, the risk of AN, BN, and EDNOS increased as the number of anti-infective agents increased and the risk of EDNOS increased as the number of hospitalizations for infections increased. Sensitivity follow-up analyses showed weaker associations between subsequent infections compared with prior infections and eating disorder risk. We continued to observe significant but attenuated risk estimates after controlling for any other psychiatric illness before the eating disorder diagnosis, suggesting that comorbidity may play a role. Taken together, our results suggest an association of infections with the pathogenesis of eating disorders.

To our knowledge, this study was the first nationwide, prospective study to report an increased risk of AN, BN, and EDNOS after hospitalizations for infections and was the largest population-based investigation to report an increased risk of AN, BN, and EDNOS after infections treated with anti-infective agents. Our results are in line with those of Raevuori et al,[11] who observed an increased use of antimicrobial medication in patients with BN and binge-eating disorder within the 5 years before eating disorder treatment. Contrary to the study by Raevuori et al[11] and earlier studies on the association between infections and AN,[34,35] our results revealed an increased risk for all eating disorder subtypes (AN, BN, and EDNOS, not just binge-eating subtypes) after use of anti-infective agents. In addition, we found that the risk of AN, BN, and EDNOS increased in association with the temporal proximity of these infections. The observed increased risks of BN and EDNOS are of similar magnitude with prior epidemiologic studies on infections and schizophrenia,[2,5,36,37] nonaffective psychosis,[38,39] and mood disorders,[3-5,37] which also found dose-response and temporal proximity associations.[2,5,36] After controlling for other psychiatric illness before the eating disorder diagnosis, we continued to observe an increased risk of BN and EDNOS of similar magnitude to those of schizophrenia,[2,5,36,37] nonaffective psychosis,[38,39] and mood disorders[3-5,37] in other studies.

The association observed with a broad range of infections provides support for the emerging immunologic hypothesis in AN[12] and, with previous work,[11,24] suggests that the immune system may also be involved in other eating disorder subtypes. The sudden onset of AN or food refusal has been reported in a small number of patients after a variety of infections, including the neurologic manifestation of acute rheumatic fever (Sydenham chorea),[40,41] streptococcal infection,[42-44] viral meningitis,[44] mycoplasma pneumonia,[44] coccidiomycosis,[45] and influenza.[44] Moreover, rapid reduced and restricted food intake after an infection is a core symptom of the pediatric acute-onset neuropsychiatric syndrome.[46] When rapid acceleration of symptom onset is preceded by a group A streptococcal infection, it is referred to as pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection.[47] Although the rate of symptom onset or the direction of effect cannot be inferred from our data, our results suggest a temporal pattern between infection and the subsequent risk of eating disorders.

Prior research has highlighted the complex interplay between the immune system and eating behaviors,[25,48] but only recently has its role in eating disorder development been investigated. Infections and inflammation alone can trigger stereotypical behavioral changes, including fever, loss of appetite, decreased food intake, and cellular hypometabolism,[49,50] through increased levels of proinflammatory cytokines, such as tumor necrosis factor and interleukins 1 and 6.[51] Infection-triggered changes in appetite could increase the risk of engaging in disordered eating behaviors in vulnerable individuals. Furthermore, infections and ingestion of anti-infective agents can alter the stability of the gut microbiota and, as a result, could affect mood and behavior via the gut-brain axis.[52] Taken together with the current study results, continuing to explore the complex interplay among immune responses with appetite and mood regulation may help explain the association of infections and their treatment with the risk of eating disorders. Without being able to isolate the actual time of eating disorder symptom onset (vs first presentation to the health care system), we were unable to discern whether an infection triggered or accelerated the onset of an eating disorder in a child with no previous symptoms or, for example, whether subthreshold or undetected eating disorder symptoms influenced vulnerability to infection, with a threshold eating disorder developing thereafter.

Although our findings suggest that infections are associated with the subsequent diagnosis of eating disorders, other mechanisms are possible. Individuals who have a greater liability of developing eating disorders may have an increased susceptibility to infections for reasons we did not measure (see limitations below), or a third unmeasured variable, such as genetic factors, could increase the risk of both infections and eating disorders. Moreover, Duncan et al[12] recently reported, to our knowledge, the first genome-wide significant locus for AN in an area related to immune functioning. Taken together, these findings suggest that individuals who will later develop an eating disorder might exhibit subtle immunodeficiencies associated with increased susceptibility or vulnerability to infections. For example, life stressors have been found to exert immunologic priming on neuroinflammatory processes, inducing a vulnerable phenotype characterized in part by a sensitized neuroimmune microenvironment.[53] Thus, prior stress can lead to a potentiated neuroinflammatory cascade on exposure to bacterial or viral infection, including changes in mood and decreased body weight and food intake.[54] Because individuals with eating disorders report high levels of stress sensitivity and anxiety[55-57] and stress alters the neuroimmune environment, infections may place individuals with immune deficiencies at greater risk for eating disorders. The key question remains whether infections are causally involved in the development of eating disorders.

Strengths and Limitations

The population-based design, large sample size, ability to distinguish eating disorder subtypes, and reliable Danish registers[26-28,30] strengthen our results. However, some limitations within the Danish registers should be noted. The universal health insurance system in Denmark ensures equal care; however, community-based studies[58,59] suggest that more than half of eating disorder cases go undetected or undiagnosed.

The current results include only diagnosed cases of eating disorders. Although no private psychiatric hospitals in Denmark exist and the nationwide registration of mental disorders is almost complete, approximately 20% of patients are treated by private psychologists and psychiatrists in Denmark.[27] These individuals may not be captured in the Danish Psychiatric Central Research Register in the present study. We had no information on the use of anti-infective agents during hospital stays or on medication use before January 1, 1995. Our results are strengthened by sensitivity analyses on individuals with lifetime medication use data. We only included individuals born after 1989; however, based on the lifetime incidence of mental disorders,[60] we would expect to capture more than half of individuals diagnosed with an eating disorder. Thus, the cohort represents a relevant population concerning the risk of eating disorders.

The study has some limitations. The current study does not enable a causal interpretation. The observed associations could simply be a secondary symptom that occurs alongside eating disorders instead of reflecting causality. Some parents may be particularly attentive to somatic and psychiatric symptoms, resulting in frequent evaluations by health care professionals and, thus, a higher likelihood of a diagnosis of an infection or eating disorder. Anti-infective agents are probably prescribed because of signs of infection[61,62]; however, signs of infection in adolescents are largely based on parental report (eg, earache, pain). Thus, anxious parents would be more likely to take their children to a health care professional and report signs of an infection, resulting in an increase in treatment of infection and opportunity for a diagnosis of an eating disorder. Although the risk for an eating disorder after an infection may represent an epiphenomenon, residual confounding may also be present. Frequent antibiotic use may be a proxy for familial factors because several family factors also correlate with more frequent antibiotic use in children, including lack of emotional support, low parental educational level, and low socioeconomic status.[63-66] Also, we cannot confirm that individuals actually took the anti-infective medications that they were prescribed and redeemed. Adherence to anti-infective treatments is estimated to be approximately 62.2%.[61] Antibiotics are prescribed when signs of an infection are present; however, overprescription of antibiotics has been reported to be as high as 46%.[62] The results of our truncated and temporal analyses do not rule out the possibility of a bidirectional association between eating disorders and infections, such that the risk an infection increases after an eating disorder diagnosis. Because of the significant somatic morbidity associated with eating disorders, we are not able to confidently interpret the bidirectionality of the associations. To translate these findings from epidemiologic associations to underlying mechanisms and clinical prevention or treatment regimens, follow-up work is required.

Conclusions

The findings suggest that infections that require hospitalization and treatment with anti-infective agents in childhood are associated with an increased risk of AN, BN, and EDNOS. Future studies that can establish more explicit links between infections and eating disorders may aid in the diagnosis and treatment of eating disorders.

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