Original Investigation

Autoimmune Diseases and Severe Infections as Risk Factors for Mood Disorders
A Nationwide Study

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IMPORTANCE Mood disorders frequently co-occur with medical diseases that involve inflammatory pathophysiologic mechanisms. Immune responses can affect the brain and might increase the risk of mood disorders, but longitudinal studies of comorbidity are lacking.

OBJECTIVE To estimate the effect of autoimmune diseases and infections on the risk of developing mood disorders.

DESIGN Nationwide, population-based, prospective cohort study with 78 million person-years of follow-up. Data were analyzed with survival analysis techniques and adjusted for calendar year, age, and sex.

SETTING Individual data drawn from Danish longitudinal registers.

PARTICIPANTS A total of 3.56 million people born between 1945 and 1996 were followed up from January 1, 1977, through December 31, 2010, with 91 637 people having hospital contacts for mood disorders.

MAIN OUTCOMES AND MEASURES The risk of a first lifetime diagnosis of mood disorder assigned by a psychiatrist in a hospital, outpatient clinic, or emergency department setting. Incidence rate ratios (IRRs) and accompanying 95% CIs are used as measures of relative risk.

RESULTS A prior hospital contact because of autoimmune disease increased the risk of a subsequent mood disorder diagnosis by 45% (IRR, 1.45; 95% CI, 1.39-1.52). Any history of hospitalization for infection increased the risk of later mood disorders by 62% (IRR, 1.62; 95% CI, 1.60-1.64). The 2 risk factors interacted in synergy and increased the risk of subsequent mood disorders even further (IRR, 2.35; 95% CI, 2.25-2.46). The number of infections and autoimmune diseases increased the risk of mood disorders in a dose-response relationship. Approximately one-third (32%) of the participants diagnosed as having a mood disorder had a previous hospital contact because of an infection, whereas 5% had a previous hospital contact because of an autoimmune disease.

CONCLUSIONS AND RELEVANCE Autoimmune diseases and infections are risk factors for subsequent mood disorder diagnosis. These associations seem compatible with an immunologic hypothesis for the development of mood disorders in subgroups of patients.

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Mood disorders frequently co-occur with medical illnesses that involve inflammatory pathophysiologic mechanisms, such as cancer and cardiovascular diseases.[1-3] The development of mood disorders has recently been linked to inflammation,[4,5] and experimental activation of inflammatory reactions has been demonstrated to induce symptoms of mood disorders in human and animal studies.[5-9] Immune components, such as proinflammatory cytokines and brain-reactive antibodies, can induce changes in neurotransmitter and neuroendocrine function related to psychiatric disorders.[5,10,11] In addition, several studies[12] have identified diverse immune alterations in subgroups of persons with mood disorders without other known somatic comorbidities.

Inflammation is inherent to infections and autoimmune diseases. Several autoimmune diseases have been associated with mood disorders,[13-15] possibly induced by inflammation or brain-reactive antibodies.[16-18] The prime candidates for initiating autoimmunity are infections, which may cause autoantibody-mediated central nervous system (CNS) disorders.[17,19,20] The circulating brain-reactive antibodies and cytokines are particularly likely to reach the brain after compromise of the blood-CNS barriers during periods of stress, infections, and inflammation.[17,21] Indeed, CNS inflammation and blood-CNS barrier dysfunction has been observed in subgroups of patients with severe depression.[22] In addition, animal studies[23] have found that the presence of peripheral brain-reactive antibodies may induce neuropsychiatric symptoms after experimental administration of inflammation that increases the permeability of the blood-CNS barriers. Consequently, it appears that infections and autoimmune diseases can affect the brain independently and in a synergistic manner, which may ultimately increase the risk of a subsequent development of mood disorders.

Only a few smaller studies[24,25] have used longitudinal data to study the relationship between inflammation and mood disorders, and recent reviews[5,26] have emphasized the need for investigations of the link between autoimmune diseases and infections on the subsequent risk of mood disorders. To our knowledge, this is the first population-based register study on autoimmune diseases and severe infections as risk factors for the subsequent development of mood disorders.

Methods

Study Population

Data were obtained by linkage of the national Danish registers using unique personal registration numbers, which are assigned to every Dane at the time of birth.[27] The population was defined through the Danish Civil Registration System, which provides information on the date of birth, sex, and parents of all persons born in Denmark.[28] Individuals born between January 1, 1945, and December 31, 1995, and who were alive at their 16th birthday and January 1, 1977, or later, formed the study population. The cohort members were followed up from January 1, 1977, until December 31, 2010. During this period, the registers contained complete information about hospital contacts. The study cohort hence includes persons exposed to hospital contacts because of infections and autoimmune diseases from birth until age 65 year, and they are followed up for hospital contacts because of mood disorders from the age of 16 years until 65 years.

The Registers

The study population was linked to the Danish Psychiatric Central Research Register (DPCRR), which was computerized in 1969 and contains information on all admissions to Danish psychiatric inpatient facilities.[29] Information about autoimmune diseases and infections was obtained from the Danish National Hospital Registry, which contains records of all inpatients treated in Danish nonpsychiatric hospitals since 1977.[30] From 1995 onward, information regarding outpatient and emergency department contacts has been included in both registers as well. For both registers, diagnostic information was based on the *International Classification of Diseases, Eighth Revision* (*ICD-8*)[31] from 1977 to 1993 and on the *International Classification of Diseases, Tenth Revision* (*ICD-10*)[32] from 1994 to 2010. Treatment in Danish hospitals is free of charge for all residents, and there are no private psychiatric inpatient facilities in Denmark, ensuring that all psychiatric admissions are represented in the DPCRR. All personal information from the registers is anonymized when used for research purposes, and the project was approved by the Danish Data Protection Agency.

Assessment of Mood Disorders and Other Psychiatric Disorders

Cohort members were classified as having mood disorders if they had been hospitalized, had an emergency department contact, or had an outpatient contact because of an affective episode as diagnosed by the treating psychiatrist. Persons were subclassified as having bipolar affective disorder (*ICD-8* codes: 296.19, 296.39; *ICD-10* codes: F30-F31), unipolar depression (*ICD-8* codes: 296.09, 296.29, 296.99, 298.09, 300.49; *ICD-10* codes: F32-F33), psychotic depression (*ICD-10* codes: F32.3, F33.3), and a combined group of the remaining mood disorders (*ICD-8* codes: 298.19, 301.19; *ICD-10* codes: F34-F39). Date of onset was defined as the first day of the first hospital contact (inpatient or outpatient or emergency department) that led to the assignment of one of the listed diagnoses. A positive parental psychiatric history was defined as the presence of any psychiatric contact recorded in the DPCRR. Substance use diagnoses (*ICD-8* codes: 291, 294.30, 294.38, 303, 304; *ICD-10* codes: F10-F19) were identified in the DPCRR and in the Danish National Hospital Register.

Assessment of Autoimmune Disease and Infection

The time of onset of an autoimmune or infection diagnosis was defined as the first day of the hospital contact that led to the recording of a diagnosis of these diseases in the Danish National Hospital Register. Each person can have a history of more than one autoimmune disease and more than one infection. Persons were classified as having a positive history of 1 or more of the 30 autoimmune diseases listed in **Table 1** and described further in the recent article by Eaton et al[14] if they had an inpatient or outpatient contact that led to the respective diagnosis. When defining infections, we omitted all *ICD-8* diag-

Table 1. Incidence Rate Ratio of Mood Disorders Among Persons With a Hospital Contact for Infections According to the Infection Site[a]

Site of infection	Infection but No Autoimmune Disease		Infection and Autoimmune Disease	
	Incidence Rate Ratio[b] (95% CI)	No. of Case Patients[c]	Incidence Rate Ratio[b] (95% CI)	No. of Case Patients[c]
Sepsis infections	2.06 (1.85-2.29)	332	3.24 (2.61-4.03)	82
Hepatitis infections	2.82 (2.58-3.08)	494	3.01 (2.33-3.89)	58
Gastrointestinal infections	1.62 (1.58-1.66)	7598	2.52 (2.34-2.72)	676
Skin infection	1.70 (1.65-1.74)	5865	2.63 (2.43-2.84)	621
Pregnancy-related infection	1.68 (1.60-1.76)	1708	2.26 (1.90-2.69)	128
Respiratory infections	1.69 (1.65-1.74)	7035	2.72 (2.50-2.97)	527
Urogenital infections	2.05 (2.00-2.10)	7037	2.83 (2.62-3.05)	660
CNS infections	1.65 (1.54-1.78)	716	2.72 (2.17-3.42)	74
Other types of infections	1.81 (1.76-1.86)	5729	2.53 (2.32-2.75)	531
Persons without a hospital contact with infection	1 [Reference]	60 361	1.45 (1.39-1.52)	2082

Abbreviation: CNS, central nervous system.

[a] Analyses were adjusted for sex, age, and calendar period.

[b] Calculated in 9 separate analyses adjusted for sex, age, calendar period, and other infections.

[c] Individuals may have more than one diagnosis.

noses that bore the modification code "suspected" or "not found" and similar codes for the *ICD-10*. Furthermore, we censored persons with diagnoses of human immunodeficiency virus (HIV) or AIDS (*ICD-8* code: 07983; *ICD-10* codes: B20-24) from the analysis because these patients may differ from patients with other types of infections regarding substance abuse, subsequent infections, and possible psychological stigmatization. The infections were grouped as follows: sepsis infections (*ICD-8* code: 038; *ICD-10* codes: A40-A41), hepatitis infections (*ICD-8* code: 070; *ICD-10* codes: B15-B19), gastrointestinal infections (*ICD-8* codes: 000-009, 540; *ICD-10* codes: A00-A09, K35), skin infections (*ICD-8* codes: 035, 050-057, 110-111, 680-686; *ICD-10* codes: B00-B09, A46, L00-L08), respiratory infections (*ICD-8* codes: 460-486; *ICD-10* codes: J00-J18), infections related to pregnancy (*ICD-8* codes: 630, 635, 670; *ICD-10* codes: O23, O85-O86, O98, O264), urogenital infections (*ICD-8* codes: 580, 590, 595.00-595.01, 604, 612, 620, 622; *ICD-10* codes: N00, N10, N300, N390, N45, N518B, N70-N72, N76-N77), CNS infections (*ICD-8* codes: 013, 02701, 03609, 04000-04399, 045-046, 05201, 05302, 05403, 05501, 05601, 062-065, 07199, 07202, 07501, 07929, 09049, 0949, 320-324, 392, 47400; *ICD-10* codes: DA022C, DA066, DA17, DA229C, DA321, DA390, DA504, DA514B, DA521A-B, DA548A,D, DA80-DA89, DB003-DB004, DB010-DB011, DB020-DB021, DB050-DB051, DB060, DB261-DB262, DB375, DB451, DB582, DB602, DE236A, DG0, DI02, DP352A), and other types of infections (the remaining infections within the general chapters; *ICD-8* codes: 000-136; *ICD-10* codes: A, B; together with *ICD-8* code: 710; *ICD-10* code: M00). When looking at time since the last infection, we only considered the first 8 admissions for infections because of practical considerations.

Statistical Analysis

The members of the cohort were followed up until onset of a mood disorder requiring hospital contact, hospital contact for HIV or AIDS, death, emigration from Denmark, disappearance, or December 31, 2010 (whichever came first). The IRR (measures of relative risk) was estimated using Poisson regression with the GENMOD procedure in SAS statistical software, version 9.2 (SAS Institute, Inc). Age; calendar year; the occurrence of infection, autoimmune diseases, or substance use disorder; and psychiatric contacts of parents were treated as time-dependent variables, whereas all other variables were considered time independent. The *P* values and 95% CIs were based on Wald statistics. All analyses were adjusted for age, sex, and calendar year. Calendar year was categorized in 1-year periods from 1977 to 2010, and age was categorized in 1-year intervals from 16 to 67 years. The method described by Andersson et al[33] was used to calculate the synergy index. The population-attributable risk was estimated as described by Bruzzi et al.[34]

Results

The study population consisted of 3 562 260 people born in Denmark between 1945 and 1995. In this cohort, 91 637 individuals were diagnosed as having a mood disorder (55 677 females and 35 960 males) from January 1, 1977, through December 31, 2010. The total follow-up time was 77 506 581 person-years. Before the diagnosis of a mood disorder, a total of 29 194 patients (31.9%) were diagnosed as having one or more infections (19 424 females and 9770 males), 4195 (4.6%) were diagnosed as having one or more autoimmune diseases (2692 females and 1503 males), and 2113 (2.3%) were diagnosed as having an autoimmune disease and an infection (1416 females and 697 males). The population-attributable risk of mood disorders associated with hospital contacts for infections was 12.1% (ie, the proportion of mood disorder cases that could be avoided if the association with hospital contacts for infections was causal and could be eliminated). Hospital contacts for autoimmune diseases were associated with a population-attributable risk of 1.4% of the mood disorders. All analyses were adjusted for sex, age, and calendar period, unless otherwise stated.

A positive history of an infection, compared with its absence, was associated with an IRR for mood disorder of 1.63 (95% CI, 1.61-1.66). Similarly, a positive history of an autoimmune disease, compared with its absence, was associated with an IRR for mood disorder of 1.57 (95% CI, 1.52-1.62). However, when infections are excluded from the model, the IRR of mood disorders diminished to 1.45 (95% CI, 1.39-1.52). In persons with

Table 2. Incidence Rate Ratio of Mood Disorders in Persons With a Hospital Contact for Autoimmune Diseases and Infections in Denmark (1977-2010)[a]

Autoimmune Disease	Mood Disorders in Persons Without Infections		Mood Disorder in Persons With Infections	
	Incidence Rate Ratio[b] (95% CI)	No. of Case Patients	Incidence Rate Ratio[a] (95% CI)	No. of Case Patients
Persons without autoimmune disease	1 [Reference]	60 361	1.62 (1.60-1.64)	27 081
Any autoimmune disease	1.45 (1.39-1.52)	2082[c]	2.35 (2.25-2.46)	2113[b]
Autoimmune diseases with suspected presence of brain-reactive antibodies	1.58 (1.49-1.68)	1057	2.49 (2.35-2.65)	1123
Autoimmune hepatitis	2.28 (1.53-3.41)	24	3.13 (2.39-4.11)	52
Autoimmune thyroiditis	1.05 (0.72-1.52)	28	1.63 (1.09-2.43)	24
Celiac disease	1.91 (1.41-2.60)	41	1.90 (1.32-2.73)	29
Guillain-Barré syndrome	1.61 (1.14-2.26)	33	2.24 (1.58-3.17)	32
Multiple sclerosis	1.52 (1.30-1.77)	162	2.42 (2.06-2.86)	142
Sjögren syndrome	1.79 (1.23-2.61)	27	2.58 (1.79-3.71)	29
Systemic lupus erythematosus	2.16 (1.61-2.89)	45	2.19 (1.65-2.92)	47
Thyrotoxicosis, Graves disease	1.28 (1.12-1.45)	228	1.90 (1.63-2.21)	165
Type 1 diabetes mellitus	1.77 (1.61-1.94)	469	2.84 (2.62-3.07)	603
Other autoimmune diseases	1.35 (1.27-1.43)	1206	2.22 (2.08-2.36)	1282
Ankylosing spondylitis	1.23 (0.91-1.65)	44	2.02 (1.46-2.81)	36
Crohn disease	1.75 (1.52-2.01)	191	2.32 (2.04-2.65)	224
Iridocyclitis	1.22 (1.00-1.48)	101	2.08 (1.70-2.54)	94
Juvenile arthritis	1.20 (0.88-1.64)	39	2.48 (1.93-3.19)	61
Psoriasis vulgaris	1.58 (1.38-1.81)	203	2.60 (2.27-2.97)	212
Seropositive rheumatoid arthritis	1.08 (0.93-1.25)	167	2.18 (1.89-2.52)	183
Ulcerative colitis	1.41 (1.27-1.57)	331	2.27 (2.04-2.54)	315
Alopecia areata	1.08 (0.66-1.77)	16	2.43 (1.60-3.69)	22
Autoimmune hemolytic anemia	2.53 (1.27-5.06)	8	2.28 (1.02-5.07)	6
Dermatopolymyositis	1.25 (0.60-2.62)	7	3.40 (2.01-5.74)	14
Idiopathic thrombocytopenic purpura	1.18 (0.71-1.96)	15	2.13 (1.37-3.30)	20
Myasthenia gravis	1.19 (0.62-2.30)	9		4
Pernicious anemia	1.37 (0.81-2.30)	14	2.14 (1.24-3.68)	13
Primary adrenocortical insufficiency	2.58 (1.53-4.35)	14	1.64 (0.95-2.82)	13
Primary biliary cirrhosis	1.74 (0.78-3.88)	6		3
Pemphigus		2	4.31 (1.94-9.60)	6
Pemphigoid		1		1
Polymyalgia rheumatica	1.30 (0.77-2.19)	14	3.81 (2.53-5.73)	23
Scleroderma	1.03 (0.56-1.92)	10	3.18 (2.05-4.93)	20
Vitiligo	1.24 (0.70-2.17)	12	2.01 (1.14-3.54)	12
Wegener granulomatosis		2	2.37 (1.18-4.75)	8

[a] Analyses were adjusted for sex, age, and calendar period.

[b] Relative risks were not estimated when there were fewer than 5 exposed cases. Each separate autoimmune disease gave rise to one analysis adjusted for all other autoimmune diagnoses.

[c] The data reflect that an individual can have multiple autoimmune diseases.

an autoimmune disease, who also had a hospital contact for infection, the IRR of mood disorders increased to 2.35 (95% CI, 2.25-2.46). The synergy index[33] for the interaction of infections and autoimmune diseases was statistically significant at 1.27 (95% CI, 1.15-1.39), indicating that the effect on the risk of a mood disorder diagnosis is larger than what would be predicted using an additive effect of infections and autoimmune diseases. The multiplicative effect (ie, statistical interaction) was, however, not significant (IRR, 1.00; 95% CI, 0.94-1.07). Thus, the risk of mood disorders for persons with an autoimmune disease and an infection was larger than predicted by the combination of the single effects of the 2 disease groups, indicating the presence of a synergistic effect of the 2 exposures.

The IRR of mood disorders was increased irrespective of the site of infection (Table 1), with hepatitis resulting in the most elevated risk of mood disorders (IRR, 2.82; 95% CI, 2.58-3.08), followed by sepsis (IRR, 2.06; 95% CI, 1.85-2.29) and urogenital infections (IRR, 2.05; 95% CI, 2.00-2.10). The risk of mood disorders after a specific autoimmune disease was elevated for all individual autoimmune diseases and significant for most (**Table 2**). The risk of developing mood disorders was elevated the most in the group of autoimmune diseases with suspected presence of brain-reactive antibodies (IRR, 1.58; 95% CI, 1.49-1.68), particularly when combined with an infection (IRR, 2.49; 95% CI, 2.35-2.65).

Among persons with just one hospital contact for infection and no autoimmune diseases, the IRR for a subsequent

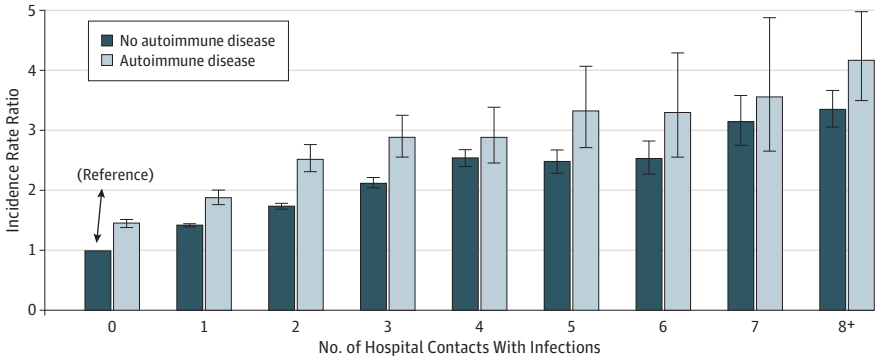
Table 3. Incidence Rate Ratios of Mood Disorders and Number of Hospital Contacts for Infections in Denmark (1977-2010)[a]

Hospital Contacts	No Autoimmune Diseases		Autoimmune Diseases	
	Incident Rate Ratio (95% CI)	No. of Cases	Incident Rate Ratio (95% CI)	No. of Cases
No. of hospital contacts with infection				
0	1 [Reference]	60 361	1.46 (1.39-1.52)	2082
1	1.43 (1.40-1.45)	15 735	1.89 (1.77-2.02)	885
2	1.74 (1.69-1.79)	5865	2.54 (2.33-2.77)	506
3	2.12 (2.04-2.21)	2565	2.90 (2.57-3.27)	270
4	2.53 (2.40-2.68)	1304	2.86 (2.42-3.37)	143
5	2.47 (2.28-2.68	603	3.35 (2.73-4.11)	93
6	2.53 (2.27-2.83)	327	3.27 (2.52-4.26)	56
7	3.14 (2.75-3.58)	223	3.62 (2.64-4.95)	39
≥8	3.36 (3.06-3.68)	459	4.12 (3.45-4.92)	121
No. of hospital contacts with different types of infections by number of infection types[b]				
1	1.47 (1.45-1.50)	19 805	2.00 (1.89-2.12)	1246
2	2.09 (2.03-2.14)	5549	2.97 (2.73-3.22)	584
3	2.84 (2.68-2.99)	1372	3.70 (3.23-4.24)	210
4	3.55 (3.16-3.99)	287	3.74 (2.87-4.89)	54
≥5	4.80 (3.78-6.09)	68	4.43 (2.83-6.95)	19

[a] Analyses were adjusted for sex, age, and calendar period.

[b] Note that these estimates represents the number of hospital contacts with different types of infections.

Figure. Incidence Rate Ratios



Incidence rate ratios, with 95% CIs (error bars), of subsequent mood disorders in persons with autoimmune diseases and infections in Denmark, 1977-2010.

mood disorder was 1.43 (95% CI, 1.40-1.45; **Table 3**). The risk of mood disorders seems to increase in a dose-response relationship with the number of infections, resulting in an IRR for mood disorders of 3.36 (95% CI, 3.06-3.68) for 8 or more hospital contacts for infections and no autoimmune diseases (**Figure**). In Table 3, results are also listed for hospital contacts with the number of different types of infections, which raises the risk of mood disorders with an IRR 4.80 (95% CI, 3.78-6.09; Table 3) in persons with 5 or more different types of infections and no autoimmune diseases.

Persons with 2 or more autoimmune diseases and a hospital contact for infection had a more elevated risk of mood disorders (IRR, 2.66; 95% CI, 2.36-3.00) than persons with 1 autoimmune disease and a hospital contact for infection (IRR, 2.31; 95% CI, 2.21-2.42).

A significant statistical interaction was found between the number of hospital contacts for infections and autoimmune diseases (P = .04) and between the number of different types of infections and autoimmune diseases (P = .04). For persons with and without autoimmune diseases there seems to be a dose-response relationship where the risk of mood disorder increases with the number of admissions and with different types of infections. Persons with 5 or more different types of infections have a higher risk of mood disorders if no autoimmune disease is present, whereas persons with fewer than 4 infections have the highest risk if autoimmune diseases are present. The risk of developing a mood disorder increased with the proximity in time of the infection (**Table 4**). A significant statistical interaction was found between autoimmune disease and time since the last infection (P = .04). The IRR of a mood disorder increased with the temporal proximity of the last infection to 4.33 (95% CI, 3.90-4.81) for persons with an autoimmune disease and 2.70 (95% CI, 2.60-2.80) for persons without an autoimmune disease, if the last infection had occurred less than 1 year earlier.

Sensitivity analyses revealed no differences between the joint effect of infections and autoimmune diseases among persons with or without substance use (P = .54) with a similar pat-

Table 4. Incidence Rate Ratio of Mood Disorders in Persons With Hospital Contacts for Infections According to the Time Since Last Hospital Contact for Infection in Denmark (1977-2010)[a]

	Infection but No Autoimmune Disease		Infection and Autoimmune Disease	
Time Since Last Severe Infection, y	Incidence Rate Ratio (95% CI)	No. of Case Patients	Incidence Rate Ratio (95% CI)	No. of Case Patients
<1	2.70 (2.60-2.80)	2851	4.33 (3.90-4.81)	352
1	2.13 (2.04-2.23)	2011	3.03 (2.64-3.47)	204
2	1.97 (1.88-2.07)	1724	2.54 (2.17-2.98)	153
3	1.83 (1.74-1.92)	1510	2.56 (2.17-3.03)	138
4	1.67 (1.58-1.77)	1297	2.56 (2.15-3.05)	127
5-9	1.61 (1.57-1.66)	5442	2.06 (1.87-2.27)	406
10-14	1.47 (1.42-1.51)	4142	2.14 (1.91-2.40)	297
>15	1.33 (1.29-1.36)	8104	1.70 (1.55-1.87)	436
Patients without a hospital contact with infection	1 [Reference]	60 361	1.45 (1.38-1.51)	2082

[a] Analyses were adjusted for sex, age, and calendar period and were based on the 8 first admissions with infection.

tern of results as the total study population when persons with substance use disorders are excluded (eTable in Supplement). Likewise, people with a psychiatric family history did not have a larger effect of autoimmune diseases and infections than persons without a psychiatric family history (P = .49). The number of hospital contacts for infection and autoimmune diseases also did not add significantly more to the increased risk of mood disorders in persons with a psychiatric family history than persons without a psychiatric family history (P = .75). However, the main effect of a psychiatric family history increases the risk of mood disorders with an IRR of 2.17 (95% CI, 2.12-2.21) compared with persons without a psychiatric family history. When the main effects of a psychiatric family history in the analysis were included, the persons with a psychiatric family history and a hospital contact for an infection had an increased IRR of mood disorders of 3.06 (95% CI, 2.96-3.14). A hospital contact for an autoimmune disease increased the risk of mood disorders (IRR, 2.68; 95% CI, 2.41-2.98), and hospital contacts for infections and autoimmune diseases increased the risk of mood disorders (IRR, 3.83; 95% CI, 3.48-4.21) in people with a psychiatric family history when compared with persons without a psychiatric family history and without hospital contacts for infection and autoimmune diseases.

Sensitivity analysis by age revealed a significant effect of age on the risk of mood disorders after an infection, with persons older than 30 years having a more elevated risk (P = .046) of mood disorders (IRR, 1.70; 95% CI, 1.67-1.73) than persons younger than 30 years (IRR, 1.53; 95% CI, 1.49-1.56). Sensitivity analysis on calendar period and between the *ICD-8* and *ICD-10* periods revealed no significant differences on the overall estimates. Also when restricting the cohort to include only persons born after 1977, when we have complete lifetime follow-up of hospital contacts in the registers, we found identical results as in the large cohort. The relative risks of a mood disorder are most elevated for women after an infection (females: IRR, 1.68; 95% CI, 1.66-1.72; males: IRR, 1.50; 95% CI 1.47-1.54; test of sex difference: P <.001), but after an autoimmune disease males have the highest IRR of mood disorders (females: IRR, 1.35; 95% CI, 1.30-1.41; males: IRR, 1.67; 95% CI, 1.59-1.76; test of sex difference: P <.001).

When studying the subtype of mood disorders, there were 79 737 persons with unipolar depression, 13 034 persons with bipolar depression, 5683 persons with psychotic depression, and 7762 persons with the remaining mood disorders during the study period (an individual might have had more than one diagnosis). Hospital contacts for infections increased the risk of bipolar disorder (IRR, 1.61; 95% CI, 1.55-1.68), unipolar depression (IRR, 1.63; 95% CI, 1.61-1.66), and psychotic depression (IRR, 1.58; 95% CI 1.49-1.68) similarly, whereas the risk of the remaining mood disorders were slightly more elevated (IRR, 1.77; 95% CI, 1.68-1.87). Autoimmune diseases increased the risk of bipolar disorder with an IRR of 1.25 (95% CI, 1.11-1.41), unipolar depression with an IRR of 1.46; (95% CI, 1.40-1.53), and the remaining group of mood disorders with an IRR of 1.76 (95% CI, 1.52-2.05), whereas the risk of psychotic depression was insignificantly increased with an IRR of 1.18 (95% CI, 0.99-1.41).

Discussion

In this national cohort study, infections and autoimmune diseases increased the risk of subsequent mood disorders in a dose-response relationship. Infections were the most common risk factor, occurring in 32% of patients before the first psychiatric contact for a mood disorder, and seem to increase the risk of mood disorders more than did the autoimmune diseases, which only occurred in 5% of the patients. The risk of mood disorders for persons with an autoimmune disease and an infection was larger than predicted by the combination of the single effects of the 2 disease groups, indicating the presence of a synergistic effect of the 2 exposures.

The possible involvement of infections as a risk factor in the pathogenesis of mood disorders has previously only been investigated in a few small studies.[25,35,36] Our results indicated that any history of hospitalization for infection increased the risk of mood disorders by 62%. The risk of mood disorders increased with the temporal proximity of the last infection, especially in persons with autoimmune diseases for whom an infection within the last year increased the risk of mood disorders more than 4 times, suggesting that the re-

sults might be due to a contemporary inflammatory process. Hospital contacts for infections increased the risk of mood disorders in a dose-response relationship, with individuals with 5 or more hospital contacts with different types of infections having an increased risk of subsequent mood disorders of almost 5 times. The population-attributable risk associated with hospital contacts for infections accounted for 12% of the mood disorder cases in the present study. It remains unclear whether the results can be generalized to the more frequently occurring less severe infections and mood disorders treated by the general practitioner or to those going untreated because only hospital contacts are included in the Danish national registers. The severe infections are probably more likely to affect the brain than the less severe infections because of a more extensive inflammatory response. However, a recent study[35] has demonstrated associations of seropositivity for influenza and coronaviruses with mood disorders, and in accordance with our findings, similar associations with bipolar disorder and unipolar depression were detected. Another smaller study[25] found an association between infections in early life and the occurrence of a broad range of mental disorders, including major depression, during youth.

Several autoimmune diseases have previously been associated with mood disorders in smaller studies,[13,15,37] and elevated autoantibody levels and increased autoantibody reactivity have been observed in subgroups of patients with severe depression.[17,38] In a population-based study, Eaton et al[14] found a 70% increased risk of developing bipolar disorder (n = 9920) within 4 years of an autoimmune disease diagnosis and a 20% increased risk in the time span from 5 years onward after the diagnosis compared with the background population. Our analysis included 91 637 patients with mood disorder and found that autoimmune diseases were associated with an increased risk of mood disorders by 57%, but when separating the effect of infections, the increased risk was reduced to 45%. The risk estimates were primarily driven by unipolar depression that amounted to clearly the most cases, with an increased risk of 46% after a hospital contact with an autoimmune disease, whereas the risk of bipolar disorder was increased by 25%. In persons with a hospital contact for autoimmune diseases and infections, the risk of developing mood disorders was increased 2.35 times. The significant synergy index detected in this study may indicate a biological interaction between autoimmune diseases and infections[39,40] but needs to be interpreted cautiously because this interpretation of the synergy index rests on the assumption of no residual confounding from unmeasured or unknown risk factors for mood disorders that are unevenly distributed across the exposure groups.[41]

The associations found in this study suggest that autoimmune diseases and infections are important etiologic factors in the development of mood disorders in subgroups of the patients possibly because of the effects of inflammatory activity. Systemic inflammation can induce a "sickness behavior," with symptoms of fatigue, reduced appetite, apathy, decreased social interaction, impaired concentration, and sleep disturbances.[5] Many of these symptoms are similar to symptoms of depression, and studies[8] have suggested that in vulnerable individuals prolonged sickness behavior can progress to depression. The sickness behavior could be explained from an evolutionary perspective as an appropriate response to inflammation to release energy for the immune system and to reduce the spreading of infectious diseases.[5] The behavioral changes in sickness behavior are probably coordinated by the CNS and initiated by peripheral signals that reach particular brain centers.[42] Innate and adaptive immune responses might be involved, and there are many different routes of communication between the periphery and the brain, such as stimulation of peripheral nerves and immune components, that can induce synthesis of proinflammatory molecules in the CNS.[5] The increased inflammation that occurs in autoimmune diseases and infections may influence the brain through increased blood-CNS barrier permeability, making the brain vulnerable to infectious agents and immune components, such as cytokines and brain-reactive antibodies. In support of this hypothesis, the risk of developing a mood disorder was elevated the most in the group with autoimmune diseases and a suspected presence of brain-reactive antibodies and infections. Furthermore, proinflammatory cytokines can affect the tryptophan-kynurenine pathway, which regulates serotonin production and *N*-methyl-D-aspartate glutamate receptor activity.[5,43] Activation of the immune system additionally increases the activity of the hypothalamic-pituitary-adrenal axis, which is known to be involved in depression.[5,10] The major hormonal output of the hypothalamic-pituitary-adrenal axis is glucocorticoids, such as cortisol, which also are important regulators in the homeostatic control of the immune system.[44]

Activated inflammatory processes have also been suggested to be involved in other mental illnesses, such as schizophrenia,[45] particularly in relation to the negative and cognitive symptoms, which overlap with symptoms of mood disorders.[46] However, even though the present findings are similar to our previous results on schizophrenia,[45] the psychological effects of having a disease severe enough to require a hospital contact may have a greater effect on the increased risk of mood disorders than is the case for schizophrenia. The effects of hospitalization might be nonspecific and may desensitize the patient to health care professionals and increase the detection of subsequent mood disorders. However, the findings are not due to only detection bias because the elevated risk of mood disorders remained significant more than 15 years after the last hospital contact for a severe infection. In addition, hospital contacts for infections increased the risk of mood disorders more than autoimmune diseases did, which would probably require treatment for longer periods, if not lifelong treatment, opposite of many infections that can be successfully treated and eliminated. Furthermore, the group of autoimmune diseases with a suspected presence of brain-reactive antibodies was associated with higher risks of subsequent mood disorders than the group without, and several of the patients with autoimmune diseases who required hospitalization did not display a significantly increased risk of mood disorders.

Exposure to physical or psychologic stressors is also well known to increase the risk of acquiring infections[47] and enhances immune responses.[48] Patients frequently report phases of stress preceding the development of mood disorders, and

the inflammatory response might simply be a parallel finding and not a causal relationship. Inflammation-related genes have been associated with susceptibility to mood disorders,[49] and environmental influences, such as infections and autoimmune diseases, may interact with genetic factors. Nevertheless, our results suggest that persons with a psychiatric family history are not more vulnerable to developing mood disorders than persons without a psychiatric family history after a hospital contact for autoimmune diseases or infections. However, a psychiatric family history is probably too crude an indicator of variation in individual genes to exclude an effect of genetic stratification. Psychiatric family history and substance use could also represent a proxy for adverse social factors, even though in this analysis these factors do not influence the association among infections, autoimmune diseases, and the subsequent development of mood disorders. An iatrogenic effect of medical treatment seems unlikely to explain the major associations in this study because only some of the included autoimmune diseases would be treated with steroids, for instance, that may increase the risk of mood disorders, and there is no evidence of antibiotics being related to an increased risk of mood disorders. Anti-inflammatory agents have actually been suggested to improve mood symptoms in patients with inflammatory disorders and enhance responsiveness to antidepressants.[2,46,50-52]

We only included hospital contacts, and the less severe cases of infections, autoimmune diseases, and mood disorders not requiring a hospital contact could not be included, which is a limitation on the generalization of the data to those with less severe illness but also a strength regarding the actual diseases that have been severe enough to require a hospital contact. Patients with autoimmune diseases and those with mood disorders can have a long duration of untreated illness or may not require a hospital contact, which could bias the time of disease onset reported in this study. In addition, the relationship might even be bidirectional because psychological stress associated with mood disorders might also be a trigger for autoimmune disease activity and infections. Nonetheless, our findings illustrate robust associations between hospital contacts for autoimmune diseases and infections and subsequent first-time diagnosis of severe mood disorders that require a hospital contact.

In conclusion, autoimmune diseases and the number of severe infections are independent and synergistic risk factors for mood disorders, with hospital-treated infections being the most common risk factor, with a population-attributable risk of 12% in this national cohort. These associations are compatible with the hypothesis of a general immunologic response affecting the brain in subgroups of patients with mood disorders. Although the hypothesis of an immunologic contribution is interesting, it remains unclear precisely how the immunologic process affects the brain and whether it is a causal relationship or an epiphenomenon of underlying genetic, psychological, or non–immune-related mechanisms.

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REFERENCES

1. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet*. 2007;370(9590):851-858.

2. Miller AH. Depression and immunity: a role for T cells? *Brain Behav Immun*. 2010;24(1):1-8.

3. Benros ME, Laursen TM, Dalton SO, Mortensen PB. Psychiatric disorder as a first manifestation of cancer: a 10-year population-based study. *Int J Cancer*. 2009;124(12):2917-2922.

4. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med*. 2009;71(2):171-186.

5. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci*. 2008;9(1):46-56.

6. Eisenberger NI, Berkman ET, Inagaki TK, Rameson LT, Mashal NM, Irwin MR. Inflammation-induced anhedonia: endotoxin reduces ventral striatum responses to reward. *Biol Psychiatry*. 2010;68(8):748-754.

7. Harrison NA, Brydon L, Walker C, Gray MA, Steptoe A, Critchley HD. Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. *Biol Psychiatry*. 2009;66(5):407-414.

8. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol*. 2006;27(1):24-31.

9. Reichenberg A, Yirmiya R, Schuld A, et al. Cytokine-associated emotional and cognitive disturbances in humans. *Arch Gen Psychiatry*. 2001;58(5):445-452.

10. Rivest S. Interactions between the immune and neuroendocrine systems. *Prog Brain Res*. 2010;181:43-53.

11. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol Psychiatry*. 2009;65(9):732-741.

12. Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major depression. *Biol Psychiatry*. 2010;67(5):446-457.

13. Korczak DJ, Pereira S, Koulajian K, Matejcek A, Giacca A. Type 1 diabetes mellitus and major depressive disorder: evidence for a biological link. *Diabetologia*. 2011;54(10):2483-2493.

14. Eaton WW, Pedersen MG, Nielsen PR, Mortensen PB. Autoimmune diseases, bipolar disorder, and non-affective psychosis. *Bipolar Disord*. 2010;12(6):638-646.

15. Gold SM, Irwin MR. Depression and immunity: inflammation and depressive symptoms in multiple sclerosis. *Immunol Allergy Clin North Am*. 2009;29(2):309-320.

16. Katzav A, Solodeev I, Brodsky O, et al. Induction of autoimmune depression in mice by anti-ribosomal P antibodies via the limbic system. *Arthritis Rheum*. 2007;56(3):938-948.

17. Diamond B, Huerta PT, Mina-Osorio P, Kowal C, Volpe BT. Losing your nerves? maybe it's the antibodies. *Nat Rev Immunol*. 2009;9(6):449-456.

18. Chen P, Jiang T, Ouyang J, Chen Y. Depression, another autoimmune disease from the view of autoantibodies. *Med Hypotheses*. 2009;73(4):508-509.

19. Rose NR. The role of infection in the pathogenesis of autoimmune disease. *Semin Immunol*. 1998;10(1):5-13.

20. Margutti P, Delunardo F, Ortona E. Autoantibodies associated with psychiatric disorders. *Curr Neurovasc Res*. 2006;3(2):149-157.

21. Irani S, Lang B. Autoantibody-mediated disorders of the central nervous system. *Autoimmunity*. 2008;41(1):55-65.

22. Bechter K, Reiber H, Herzog S, Fuchs D, Tumani H, Maxeiner HG. Cerebrospinal fluid analysis in affective and schizophrenic spectrum disorders: identification of subgroups with immune responses and blood-CSF barrier dysfunction. *J Psychiatr Res*. 2010;44(5):321-330.

23. Kowal C, DeGiorgio LA, Nakaoka T, et al. Cognition and immunity; antibody impairs memory. *Immunity*. 2004;21(2):179-188.

24. Pasco JA, Nicholson GC, Williams LJ, et al. Association of high-sensitivity C-reactive protein with de novo major depression. *Br J Psychiatry*. 2010;197(5):372-377.

25. Goodwin RD. Association between infection early in life and mental disorders among youth in the community: a cross-sectional study. *BMC Public Health*. 2011;11:878.

26. Leboyer M, Soreca I, Scott J, et al. Can bipolar disorder be viewed as a multi-system inflammatory disease? *J Affect Disord*. 2012;141(1):1-10.

27. Frank L. Epidemiology. The epidemiologist's dream: Denmark. *Science*. 2003;301(5630):163.

28. Pedersen CB, Gøtzsche H, Møller JO, Mortensen PB. The Danish Civil Registration System: a cohort of eight million persons. *Dan Med Bull*. 2006;53(4):441-449.

29. Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. *Scand J Public Health*. 2011;39(7)(suppl):54-57.

30. Andersen TF, Madsen M, Jørgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register: a valuable source of data for modern health sciences. *Dan Med Bull*. 1999;46(3):263-268.

31. World Health Organization. Klassifikation af sygdomme; Udvidet dansk-latinsk udgave af verdenssundhedsorganisationens internationale klassifikation af sygdomme, 8 revision, 1965 *[*Classification of Diseases: Extended Danish-Latin version of the World Health Organization International Classification of Diseases, 8th revision, 1965*]*. Copenhagen, Denmark: World Health Organization; 1971.

32. World Health Organization. WHO ICD-10: Psykiske lidelser og adfærdsmæssige forstyrelser: Klassifikation og diagnosekriterier *[*WHO ICD-10: Mental and Behavioural Disorders: Classification and Diagnostic Criteria*]*. Copenhagen, Denmark: World Health Organization; 1994.

33. Andersson T, Alfredsson L, Källberg H, Zdravkovic S, Ahlbom A. Calculating measures of biological interaction. *Eur J Epidemiol*. 2005;20(7):575-579.

34. Bruzzi P, Green SB, Byar DP, Brinton LA, Schairer C. Estimating the population attributable risk for multiple risk factors using case-control data. *Am J Epidemiol*. 1985;122(5):904-914.

35. Okusaga O, Yolken RH, Langenberg P, et al. Association of seropositivity for influenza and coronaviruses with history of mood disorders and suicide attempts. *J Affect Disord*. 2011;130(1-2):220-225.

36. Steiner J, Bogerts B, Sarnyai Z, et al. Bridging the gap between the immune and glutamate hypotheses of schizophrenia and major depression: potential role of glial NMDA receptor modulators and impaired blood-brain barrier integrity. *World J Biol Psychiatry*. 2012;13(7):482-492.

37. Padmos RC, Bekris L, Knijff EM, et al. A high prevalence of organ-specific autoimmunity in patients with bipolar disorder. *Biol Psychiatry*. 2004;56(7):476-482.

38. Laske C, Zank M, Klein R, et al. Autoantibody reactivity in serum of patients with major depression, schizophrenia and healthy controls. *Psychiatry Res*. 2008;158(1):83-86.

39. Darroch J. Biologic synergism and parallelism. *Am J Epidemiol*. 1997;145(7):661-668.

40. van Os J, Rutten BP, Poulton R. Gene-environment interactions in schizophrenia: review of epidemiological findings and future directions. *Schizophr Bull*. 2008;34(6):1066-1082.

41. Greenland S. Basic problems in interaction assessment. *Environ Health Perspect*. 1993;101(suppl 4):59-66.

42. Perry VH, Cunningham C, Holmes C. Systemic infections and inflammation affect chronic neurodegeneration. *Nat Rev Immunol*. 2007;7(2):161-167.

43. Raison CL, Dantzer R, Kelley KW, et al. CSF concentrations of brain tryptophan and kynurenines during immune stimulation with IFN-alpha: relationship to CNS immune responses and depression. *Mol Psychiatry*. 2010;15(4):393-403.

44. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids: new mechanisms for old drugs. *N Engl J Med*. 2005;353(16):1711-1723.

45. Benros ME, Nielsen PR, Nordentoft M, Eaton WW, Dalton SO, Mortensen PB. Autoimmune diseases and severe infections as risk factors for schizophrenia: a 30-year population-based register study. *Am J Psychiatry*. 2011;168(12):1303-1310.

46. Meyer U, Schwarz MJ, Müller N. Inflammatory processes in schizophrenia: a promising neuroimmunological target for the treatment of negative/cognitive symptoms and beyond. *Pharmacol Ther*. 2011;132(1):96-110.

47. Pedersen A, Zachariae R, Bovbjerg DH. Influence of psychological stress on upper respiratory infection: a meta-analysis of prospective studies. *Psychosom Med*. 2010;72(8):823-832.

48. García-Bueno B, Caso JR, Leza JC. Stress as a neuroinflammatory condition in brain: damaging and protective mechanisms. *Neurosci Biobehav Rev*. 2008;32(6):1136-1151.

49. Shelton RC, Claiborne J, Sidoryk-Wegrzynowicz M, et al. Altered expression of genes involved in inflammation and apoptosis in frontal cortex in major depression. *Mol Psychiatry*. 2011;16(7):751-762.

50. Tyring S, Gottlieb A, Papp K, et al. Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomised phase III trial. *Lancet*. 2006;367(9504):29-35.

51. Henry CJ, Huang Y, Wynne A, et al. Minocycline attenuates lipopolysaccharide (LPS)-induced neuroinflammation, sickness behavior, and anhedonia. *J Neuroinflammation*. 2008;5:15.

52. Raison CL, Rutherford RE, Woolwine BJ, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. *JAMA Psychiatry*. 2012;70(1):31-41.