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DOI: 10.5498/wjp.v6.i4.419

World J Psychiatr 2016 December 22; 6(4): 419-430
ISSN 2220-3206 (online)
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ORIGINAL ARTICLE

Retrospective Study

Infectious, atopic and inflammatory diseases, childhood adversities and familial aggregation are independently associated with the risk for mental disorders: Results from a large Swiss epidemiological study

Vladeta Ajdacic-Gross, Aleksandra Aleksandrowicz, Stephanie Rodgers, Margot Mutsch, Anja Tesic, Mario Müller, Wolfram Kawohl, Wulf Rössler, Erich Seifritz, Enrique Castelao, Marie-Pierre F Strippoli, Caroline Vandeleur, Roland von Känel, Rosa Paolicelli, Markus A Landolt, Cornelia Witthauer, Roselind Lieb, Martin Preisig

Vladeta Ajdacic-Gross, Aleksandra Aleksandrowicz, Stephanie Rodgers, Anja Tesic, Mario Müller, Wolfram Kawohl, Wulf Rössler, Erich Seifritz, Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zurich, 8021 Zurich, Switzerland

Margot Mutsch, Epidemiology, Biostatistics and Prevention Institute, University of Zurich, 8001 Zurich, Switzerland

Enrique Castelao, Marie-Pierre F Strippoli, Caroline Vandeleur, Martin Preisig, Department of Psychiatry, University Hospital of Lausanne, 1011 Lausanne, Switzerland

Roland von Känel, Department of Neurology, Bern University Hospital, 3010 Bern, Switzerland

Roland von Känel, Clinic Barmelweid, 5017 Barmelweid, Switzerland

Rosa Paolicelli, Division of Psychiatry Research, University of Zurich, 8032 Zurich, Switzerland

Markus A Landolt, University Children's Hospital Zurich and Children's Research Center and Division of Child and Adolescent Health Psychology, Department of Psychology, University of Zurich, 8032 Zurich, Switzerland

Cornelia Witthauer, Roselind Lieb, Department of Psychology, Division of Clinical Psychology and Epidemiology, University of Basel, 4055 Basel, Switzerland

Author contributions: Preisig M, Castelao E, Strippoli MPF and Vandeleur C designed the PsyCoLaus study and acquired the data; Ajdacic-Gross V, Aleksandrowicz A, Rodgers S and Müller M carried out the analysis; all authors contributed to the interpretation of the results and to the critical revision of the manuscript; Ajdacic-Gross V and Aleksandrowicz A wrote the paper; all authors contributed critical revisions of the text.

Supported by Research grants from GlaxoSmithKline; the Faculty of Biology and Medicine of Lausanne; and the Swiss National Science Foundation, Nos. 3200B0-105993, 3200B0-118308, 33CSCO-122661, 33CS30-139468 and 33CS30-148401.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee of the University of Lausanne.

Informed consent statement: All participants gave their written informed consent at enrollment into the study.

Conflict-of-interest statement: All authors: None.

Data sharing statement: The participants gave informed consent for data sharing within CoLaus and PsyCoLaus. No additional data is available.

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Manuscript source: Invited manuscript

Correspondence to: Vladeta Ajdacic-Gross, PhD, Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric

Hospital, University of Zurich, PO Box 2019, 8021 Zurich, Switzerland. vajdacic@dgsp.uzh.ch
Telephone: +41-44-2967433
Fax: +41-44-2967449

Received: June 28, 2016
Peer-review started: July 1, 2016
First decision: August 5, 2016
Revised: September 12, 2016
Accepted: October 5, 2016
Article in press: October 9, 2016
Published online: December 22, 2016

Abstract

AIM

To examine the associations between mental disorders and infectious, atopic, inflammatory diseases while adjusting for other risk factors.

METHODS

We used data from PsyCoLaus, a large Swiss Population Cohort Study (n = 3720; age range 35-66). Lifetime diagnoses of mental disorders were grouped into the following categories: Neurodevelopmental, anxiety (early and late onset), mood and substance disorders. They were regressed on infectious, atopic and other inflammatory diseases adjusting for sex, educational level, familial aggregation, childhood adversities and traumatic experiences in childhood. A multivariate logistic regression was applied to each group of disorders. In a complementary analysis interactions with sex were introduced *via* nested effects.

RESULTS

Associations with infectious, atopic and other chronic inflammatory diseases were observable together with consistent effects of childhood adversities and familial aggregation, and less consistent effects of trauma in each group of mental disorders. Streptococcal infections were associated with neurodevelopmental disorders (men), and measles/mumps/rubella-infections with early and late anxiety disorders (women). Gastric inflammatory diseases took effect in mood disorders (both sexes) and in early disorders (men). Similarly, irritable bowel syndrome was prominent in a sex-specific way in mood disorders in women, and, moreover, was associated with early and late anxiety disorders. Atopic diseases were associated with late anxiety disorders. Acne (associations with mood disorders in men) and psoriasis (associations with early anxiety disorders in men and mood disorders in women) contributed sex-specific results. Urinary tract infections were associated with mood disorders and, in addition, in a sex-specific way with late anxiety disorders (men), and neurodevelopmental and early anxiety disorders (women).

CONCLUSION

Infectious, atopic and inflammatory diseases are important risk factors for all groups of mental disorders. The sexual dimorphism of the associations is pronounced.

Key words: Neurodevelopmental disorders; Mental disorders; Substance abuse; Childhood diseases; Infectious diseases; Atopic diseases; Chronic inflammatory diseases; Risk factors

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Core tip: This study adds to the evidence that infectious, atopic and inflammatory diseases make up an important group of risk factors for neurodevelopmental and common mental disorders. They contribute independently of further major risk factors such as childhood adversities, traumatic experiences and familial aggregation. Each group of mental disorders (neurodevelopmental, early and late anxiety, mood, substance) attracts different combinations of risk factors. The sexual dimorphism of the associations is pronounced. The hypothesized biological mechanism that acts as a common denominator in this group of risk factors involves imbalances, *e.g.*, within the development of the immune system interfering with critical stages of brain development.

Ajdacic-Gross V, Aleksandrowicz A, Rodgers S, Mutsch M, Tesic A, Müller M, Kawohl W, Rössler W, Seifritz E, Castelao E, Strippoli MPF, Vandeleur C, von Känel R, Paolicelli R, Landolt MA, Witthauer C, Lieb R, Preisig M. Infectious, atopic and inflammatory diseases, childhood adversities and familial aggregation are independently associated with the risk for mental disorders: Results from a large Swiss epidemiological study. *World J Psychiatr* 2016; 6(4): 419-430 Available from: URL: http://www.wjgnet.com/2220-3206/full/v6/i4/419.htm DOI: http://dx.doi.org/10.5498/wjp.v6.i4.419

INTRODUCTION

There is an increasing awareness that infectious diseases, atopies and inflammatory conditions contribute to the risk for neurodevelopmental disorders (ND) and common mental disorders (CMD). A great number of the empirical results documented below underline the eminent role of the immune system. Nevertheless considerable scepticism abounds. Among other things, it is not clear how immunological risk factors are balanced against other risk factors in ND and CMD. The main aim of this study was, therefore, to assess the associations of infectious, atopic and inflammatory diseases with ND and CMD while adjusting for socio-demographic characteristic, familial aggregation, traumatic experiences and childhood adversities. A simple vulnerability-trigger model will serve to introduce the state of empirical research, thus reducing the potential variability of single and multiple hit models to a minimal general form.

Associations related to triggering mechanisms

The most intuitive example of a triggering factor in CMD is a postinfectious condition such as fatigue[1]. Infectious mononucleosis, *i.e.*, typically an Epstein Barr virus (EBV) infection in adolescence or adulthood, is a well known cause of postinfectious fatigue. However, also several other pathogens are also able to upregulate psychiatric symptoms, such as persistent pathogens: Borna disease virus, herpes simplex virus (HSV)-1, varicella zoster virus, and *Chlamydophila trachomatis*[2]. Apart from the first attack, a reactivation of an endogenous infection can increase the risk of depression[3].

It is noteworthy that the reciprocal causal direction also exists[4,5]. Generally speaking, it is not only the case that pathogens can trigger psychiatric illness, but, conversely, that psychiatric disorders can lead to an increased risk of infection. The two should not be confounded, keeping in mind that the causal direction is not always clear[6]. The examples above illustrate a trigger mechanism of ND and CMD, *i.e.*, the second part of conventional vulnerability-trigger (or, by analogy, diathesis-stress) models.

Associations related to vulnerability mechanisms

The first part of the vulnerability-trigger model are vulnerability factors occurring very early in life: Infections, atopic and inflammatory processes that establish, apart from their immediate effects, a lasting, possibly life-long vulnerability for CMD. A well known example of an early vulnerability is comprised in the pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) model. This model has been applied in attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), and tic disorders such as the Gilles de la Tourette Syndrome[7,8]. It suggests that some persons with ND or CMD might actually suffer from an autoimmune disorder due to autoantibodies directed against basal ganglia tissue and appearing after infections with group A streptococci.

Evidence for associations between early infections and ND and CMD goes far beyond PANDAS and other autoimmune processes such as NMDA receptor encephalitis[9]. A compelling example is the link between EBV infections in childhood and risk of psychotic experiences in adolescence demonstrated in the ALSPAC cohort[10]. In a similar vein, studies from the Goodwin group which suggested that respiratory diseases in childhood and severe infections requiring the use of antibiotics in the first year of life increase the risk for several mental disorders such as depression, anxiety disorders and oppositional defiant disorder (ODD) later on in life[11,12].

The temporal sequence between pathogens and CMD may apply later in life as well. For instance, Danish record linkage studies have shown that individuals hospitalized because of an infection, particularly a bacterial infection, were more likely to develop schizophrenia later in life[13]. Apart from studies demonstrating a temporal sequence, many cross-sectional antibody based studies have pointed at associations between ND and CMD and selected pathogens. Serological studies have been particularly proliferative in psychosis research by implicating a broad spectrum of viral, bacterial and protozoan pathogens. For illustrative purposes, these are: (1) herpes viridae (cytomegalovirus[14], human herpesvirus-6[15], HSV-1[16,17], EBV[18]); (2) Toxoplasma gondii[14,19-23]; (3) Chlamydia infections: trachomatis[23,24], psittaci and pneumoniae[25,26]; (4) Mycoplasma pneumoniae (case study)[27]; (5) *Helicobacter pylori*[28]; and (6) gastrointestinal pathogens[29,30].

Associations related to parallel mechanisms

Not only were pathogens shown to precede psychotic experiences but also atopic diseases such as asthma and atopic dermatitis[31]. Similarly, the first occurrence of atopic dermatitis was reported to precede major depressive disorder and anxiety disorders[32] or ADHD[33]. Also other atopic diseases preceded ADHD[34]. However, evidence for the converse temporal sequence between atopic diseases and ND and CMD was also found with ND and CMD occuring first[35,36].

Again, the number of cross-sectional comorbidity studies providing evidence for a simple link between ND and CMD on the one hand and atopic diseases on the other is much greater than those focusing on temporal succession. They involve in particular asthma[37-44], hay fever[45], and eczema[46]. The association between atopic dermatitis and ADHD has gained particular attention since it emerges typically in the first years of life[33,47,48].

Beside atopies, chronic or relapsing inflammatory diseases have been shown to be linked to a great variety of CMD, and both theoretically qualify as triggers and as vulnerability markers. Skin diseases such as acne[49,50], psoriasis[51] and rosaceae[52] also contribute to the list of associations. Moreover, this list includes gastric inflammatory diseases[53-56], and gastrointestinal diseases/syndromes: Irritable bowel syndrome[57,58], Crohn's disease[59], interstitial cystistis[60,61] as well as recurrent cystitis[62], autoimmune diseases[63-65] and others[51]. This is only a small selection of associations, and the list could be extended with ease.

Aims of the analysis

To summarize, the complex picture of associations entails any variant of temporal sequences and almost any combination between groups of somatic diseases and groups of ND and CMD. Thus, in so far as infectious, atopic and chronic inflammatory diseases precede ND and CMD or share a mutual vulnerability with them, the relevant mechanisms cannot be determined on the level of single pathogens. Taken together, the literature provides important pieces of a larger puzzle with, however, still blurred contours. Comprehensive analyses enabling a broader understanding of these links are still missing. The present study takes advantage of a

large epidemiological data base from the PsyCoLaus study[66] to further investigate whether major groups of infectious, atopic and inflammatory diseases are associated with major groups of mental disorders.

MATERIALS AND METHODS

The Colaus/PsyCoLaus study

The data used in this analysis stem from CoLaus/PsyCoLaus[66,67], a cohort study designed to study mental disorders and cardio-vascular risk factors in the community and to determine their associations. The sample was randomly selected from the residents of the city of Lausanne (Switzerland) from 2003 to 2006 according to the civil register. Sixty-seven percent of the 35 to 66 years old participants of the physical baseline exam (n = 5535) also accepted the psychiatric evaluation, which resulted in a sample of 3720 individuals who underwent both the somatic and psychiatric exams.

Measures

A French version of the semi-structured Diagnostic Interview for Genetic Studies (DIGS)[68] was used in the PsyCoLaus study to assess a broad spectrum of lifetime DSM-IV Axis I criteria. The French version has shown excellent inter-rater and adequate test-retest reliability for major mood and psychotic disorders[69] as well as for substance use disorders[70]. Moreover, the DIGS allowed for gathering additional information on the course and chronology of comorbid features[66]. However, the brief phobia section of the DIGS was replaced by the corresponding sections from the Schedule for Affective Disorders and Schizophrenia - Lifetime Version (SADS-L)[71] in the current study. The anxiety sections of the French version of the SADS-L also revealed satisfactory reliability[72]. All diagnoses were lifetime diagnoses.

Grouping of mental disorders

We considered the following major groups of mental disorders based on the typical age of onset and common classifications: (1) neurodevelopmental diseases [typically starting during childhood: Tic disorders, ADHD, conduct disorder (CD), ODD]; (2) early-onset anxiety disorders (typically starting during childhood: separation anxiety disorder, overanxious disorder, animal phobias, social phobia); (3) late-onset anxiety disorders [typically starting after adolescence: Generalized anxiety disorder (GAD), panic, agoraphobia, specific phobias (excl. animal phobias[73])]; (4) mood disorders (typically starting after adolescence: major depressive disorder, dysthymia, bipolar disorders); and (5) substance use disorders (typically starting after adolescence: alcohol, cannabis, other illicit drug abuse/dependence).

Disorders with low frequencies (schizophrenia, schizoaffective disorders) or inadequately fitting in with the major groups (OCD, personality disorders, eating disorders) were not included in the analyses.

Assessment of infectious, atopic and inflammatory diseases

The information on infectious diseases and related conditions was derived using an extended version of the medical history parts of the DIGS and the SADS-L and was based on self-reporting. In the interview participants were asked questions about ever having been diagnosed with various infectious diseases, diseases of the nervous system, cardiovascular, respiratory, gastrointestinal, metabolic and dermatological conditions as well as allergies and hormonal problems. For each disease, a screening question was asked and followed up in the case of an affirmative response.

In the current analyses the infectious diseases and related conditions were selected: (1) diseases typically related to streptococcal infections of the respiratory tract (scarlet fever, tonsillitis, rheumatic fever); (2) measles/mumps/rubella (MMR); the age range of the sample implies that most participants had not received an MMR vaccine in childhood, as routine measles and later MMR vaccinations schedules were only introduced by the Swiss government only in the 1960s; (3) urinary tract infections (UTIs) (cystitis, pyelitis, pyelonephritis, other nephritis, urethritis, prostatitis); (4) irritable bowel syndrome; (5) peptic ulcer/gastritis; (6) asthma and atopic diseases; (7) acne; and (8) psoriasis.

Covariates

We adjusted the analysis for the following variables which might account for the relationship between infectious diseases and mental disorders: (1) sex; (2) education level (low: Basic school and apprenticeship level; medium: Pre-university and high-level technical schools; high: University); (3) familial aggregation assessed by the semi-structured Family History - Research Diagnostic Criteria[74,75] which includes information on first and second degree relatives; subtypes parallelized to the groups of mental disorders mentioned above; dichotomized into any *vs* none; (4) childhood adversities dichotomized into any *vs* none if one of the following questions was confirmed: Did your parents fight frequently amongst themselves (interparental violence)?; Did your parents ever do anything that frightened you (like lock you in a closet)? (fear of maltreatment by parents); Did any of the following occur before your 16th birthday: .... put in foster care? (foster care); Overall, how would you characterize your childhood (N/A, happy, either happy not unhappy, unhappy, very unhappy)? categorized as yes, if unhappy or very unhappy (unhappy children); and (5) traumatic experiences in childhood below the age of 10 (serious accident or disaster, victim of violent attacks (self or loved ones), witnessed homicide or other forms of violent deaths; the age limit was chosen in order to focus on experiences mostly generating a vulnerability for mental disorders instead of acting as a trigger

themselves); the questions were taken from the French version of the SADS-LA (see above) and dichotomized into any *vs* none.

Statistical analysis

The data were analyzed using binary logistic regression and displaying odds ratios (OR) and 95%CI. The regression analysis was redone for men and women separately before including interaction effects. In order to better figure out the source of sex-specific divergences - either men or women - the interaction effects were modeled *via* nested effects, *i.e*., by nesting each infectious, atopic and inflammatory variable in men and in women. All analyses were carried out using SAS version 9.3. The statistical analysis was reviewed by Viktor von Wyl from the Epidemiology, Biostatistics and Prevention Institute of the University of Zürich.

RESULTS

Table 1 shows the overall and sex-specific prevalence estimates for five major groups of mental disorders (neurodevelopmental, early-onset anxiety, late-onset anxiety, mood and substance disorders) together with education level, familial aggregation, trauma below the age of 10, childhood adversities and various infectious and atopic/inflammatory diseases. In bivariate analyses, mental disorders were consistently associated with familial aggregation, trauma and childhood adversities. Trauma showed distinct sex-specific associations in early disorders and in substance abuse. The associations of ND and CMD with infectious, atopic and inflammatory diseases spread across the whole table in a less consistent way. Moreover, they displayed more sex-specific divergencies. Therefore, and since some variables, *e.g*., UTI, are skewed by sex, an additional look at the sex-specific associations was necessary in multivariate analyses.

In multivariate analysis (Table 2), the associations with familial aggregation and childhood adversities remained relatively stable across all five models for each group of mental disorders (ORs up to 3). The effect of trauma clearly diminished. Each group of ND /CMD displayed associations with any of the infectious, atopic and inflammatory diseases included in the analysis. Many associations occurred at trend level, thus suggesting more in-depth analyses either related to sex-specific associations or to the level of specific disorders.

Analyses involving interaction effects by nesting infectious, atopic and inflammatory diseases within sex (Table 3) uncovered further hetereogenity. In detail, ND disorders were associated with streptococcal infections specifically in men (OR = 1.98, 95%CI: 1.08-3.66) but not in women. Peptic ulcer/gastritis was significant only in the men model (OR = 1.95, 95%CI: 1.08-3.53), and showed a similar tendency in women. The opposite applies for UTI, where only women (OR = 1.68, 95%CI: 1.11-2.54) reached the conventional significance level.

Early-onset anxiety disorders showed associations with MMR, which were similar in both groups; again only women (OR = 1.46, 95%CI: 1.01-2.10) reached the conventional significance level. Another shared issue is irritable bowel syndrome with a strong impact in men (OR = 3.15, 95%CI: 1.58-6.28) and a trend level impact in women. Associations found specifically in men comprise peptic ulcer/gastritis (OR = 1.85, 95%CI: 1.13-3.05), psoriasis (OR = 2.02, 95%CI: 1.20-3.39) and, at trend level, acne. Moreover, associations with UTI emerged specifically in women (OR = 1.44, 95%CI: 1.16-1.79), at trend level also with atopic disease, but not in men.

In late-onset anxiety disorders, UTI (OR = 2.13, 95%CI: 1.19-3.82) were predictive not in women but in men. The significant predictors in women comprise MMR (OR = 1.81, 95%CI: 1.12-2.90) and peptic ulcer/gastritis (OR = 1.60, 95%CI: 1.02-2.51), whereas irritable bowel syndrome and atopic disease remain significant at the trend level.

Mood disorders were associated with UTI in women (OR = 1.47, 95%CI: 1.19-1.81) and in men (OR = 1.63, 95%CI: 1.00-2.65). Also the impact of peptic ulcer/gastritis is apparent in both groups (in women: OR = 1.58, 95%CI: 1.02-2.46, and in men: OR = 1.98, 95%CI: 1.26-3.09). Acne (1.96, 95%CI: 1.35-2.85) predicts mood disorders in men, whereas irritable bowel syndrome (OR = 2.25, 95%CI: 1.35-3.76) and psoriasis (OR = 2.02, 95%CI: 1.14-3.58) contribute in women.

Finally, substance abuse/dependence did not yield any relevant associations in women. In men, it was linked with peptic ulcer/gastritis (OR = 1.88, 95%CI: 1.18-2.99) and with acne (OR = 1.74, 95%CI: 1.17-2.59).

As a side effect of the analysis involving interaction effects, the sex main effect in early and late anxiety disorders disappeared and greatly diminished in mood disorders. The models proved to be stable even when the strongest predictors in each model were omitted. Preliminary analyses on a more detailed level focusing on specific ND and CMD revealed a heterogeneity of results that clearly surpassed the findings presented in this study (results not shown).

DISCUSSION

This is the first study to apply a comprehensive epidemiological perspective on the associations of major groups of ND and CMD with infectious, atopic and inflammatory diseases. It adds to the evidence that infectious, atopic and inflammatory diseases make up an important group of risk factors. The main outcome was the great range of associations although the statistical models had been adjusted for trauma, childhood adversities, familial aggregation and education. Provided that the analyses were carried out on grouped CMD and somatic diseases, the results reported in this study represent only the tip of an iceberg. In addition,

Table 1 Groups of mental disorders and risk factors in the PsyCoLaus study: Frequencies and crude odds ratios (with 95%CI), overall and by sex

	n (%)	Education level low	Education level medium	Education level high	Familial aggregation[6]	Trauma below age of 10	Childhood adversities[7]	Streptococcal diseases[8]	MMR	Peptic ulcer/ gastritis	Irritable bowel syndrome	Atopic diseases	Acne	Psoriasis	Urinary tract infections[9]
Total *n* (%)															
All	3720 (100.0)	1965 (53.4)	916 (24.9)	798 (21.7)	2071 (55.7)	160 (4.3)	1013 (27.2)	230 (6.2)	3033 (86.7)	317 (6.5)	187 (3.8)	2129 (43.8)	474 (9.7)	220 (4.5)	844 (22.7)
Males	1750 (47.0)	888 (51.3)	366 (21.1)	477 (27.6)	876 (50.1)	45 (2.6)	417 (23.8)	87 (5.0)	1353 (83.2)	159 (7.0)	52 (2.3)	895 (39.6)	191 (8.4)	108 (4.8)	86 (4.9)
Females	1970 (53.0)	1077 (55.3)	550 (28.2)	321 (16.5)	1195 (60.7)	115 (5.8)	596 (30.3)	143 (7.3)	1226 (89.6)	158 (6.1)	135 (5.2)	1234 (47.4)	283 (10.9)	112 (4.3)	758 (38.5)
Odds ratios															
Neurodevelop-mental disorders[1]															
All	308 (8.3)	1 (ref)	1.17 (0.89-1.55)	0.94 (0.69-1.29)	1.75 (1.26-2.42)	1.93 (1.22-3.05)	2.93 (2.31-3.71)	1.67 (1.11-2.50)	1.18 (0.83-1.67)	1.68 (1.14-2.49)	1.74 (1.07-2.83)	0.98 (0.78-1.24)	0.87 (0.59-1.29)	1.07 (0.63-1.80)	1.13 (0.86-1.48)
Males	189 (10.8)	1 (ref)	1.39 (0.96-2.00)	0.85 (0.58-1.24)	1.98 (1.27-3.10)	1.28 (0.53-3.06)	3.10 (2.27-4.23)	2.65 (1.57-4.48)	1.35 (0.87-2.08)	1.52 (0.89-2.57)	2.18 (1.03-4.61)	1.15 (0.85-1.56)	0.88 (0.50-1.53)	1.09 (0.57-2.08)	1.36 (0.73-2.56)
Females	119 (6.0)	1 (ref)	1.03 (0.67-1.57)	0.93 (0.54-1.58)	1.75 (1.08-2.85)	2.98 (1.72-5.12)	3.22 (2.21-4.69)	1.05 (0.52-2.11)	1.13 (0.63-2.04)	1.94 (1.08-3.49)	1.86 (0.97-3.58)	0.89 (0.62-1.30)	0.97 (0.55-1.72)	0.93 (0.37-2.35)	1.94 (1.34-2.82)
Early anxiety disorders[2]															
All	951 (25.6)	1 (ref)	0.98 (0.82-1.17)	0.93 (0.77-1.12)	2.75 (2.36-3.21)	1.96 (1.41-2.71)	1.85 (1.58-2.17)	1.51 (1.13-2.00)	1.43 (1.12-1.81)	1.33 (1.01-1.76)	2.42 (1.74-3.37)	1.23 (1.06-1.43)	1.32 (1.05-1.66)	1.41 (1.03-1.94)	1.90 (1.61-2.24)
Males	327 (18.7)	1 (ref)	1.03 (0.76-1.41)	1.06 (0.80-1.41)	2.48 (1.93-3.20)	2.01 (1.06-3.82)	2.01 (1.55-2.61)	1.71 (1.05-2.78)	1.27 (0.89-1.80)	1.75 (1.15-2.66)	2.84 (1.53-5.27)	1.03 (0.81-1.31)	1.59 (1.08-2.32)	2.22 (1.42-3.48)	1.25 (0.74-2.11)
Females	624 (31.7)	1 (ref)	0.90 (0.72-1.13)	1.01 (0.77-1.32)	2.76 (2.26-3.36)	1.65 (1.13-2.42)	1.65 (1.35-2.02)	1.29 (0.91-1.84)	1.35 (0.96-1.88)	1.11 (0.77-1.61)	1.97 (1.33-2.92)	1.25 (1.03-1.51)	1.11 (0.83-1.47)	1.01 (0.64-1.59)	1.51 (1.24-1.83)
Late anxiety disorders[3]															
All	554 (14.9)	1 (ref)	0.96 (0.77-1.20)	0.82 (0.64-1.04)	2.15 (1.67-2.76)	1.64 (1.12-2.42)	1.92 (1.59-2.32)	1.38 (0.98-1.94)	1.44 (1.07-1.95)	1.66 (1.21-2.27)	2.30 (1.59-3.32)	1.34 (1.12-1.61)	1.13 (0.85-1.49)	1.13 (0.75-1.69)	1.49 (1.22-1.82)
Males	200 (11.4)	1 (ref)	1.14 (0.78-1.67)	1.22 (0.87-1.72)	1.96 (1.24-3.08)	0.97 (0.38-2.48)	1.60 (1.16-2.20)	1.01 (0.51-1.99)	1.03 (0.68-1.56)	1.32 (0.77-2.25)	2.04 (0.97-4.31)	1.19 (0.89-1.61)	1.56 (0.99-2.46)	0.70 (0.33-1.47)	2.68 (1.60-4.49)
Females	354 (18.0)	1 (ref)	0.84 (0.65-1.11)	0.64 (0.45-0.92)	2.06 (1.53-2.79)	1.67 (1.08-2.57)	2.02 (1.59-2.55)	1.47 (0.98-2.20)	1.75 (1.11-2.75)	1.93 (1.29-2.86)	2.14 (1.39-3.29)	1.35 (1.07-1.69)	0.88 (0.61-1.27)	1.56 (0.95-2.56)	1.06 (0.83-1.34)
Mood disorders[4]															
All	1765 (47.4)	1 (ref)	1.21 (1.03-1.41)	0.99 (0.84-1.16)	2.14 (1.87-2.45)	1.90 (1.37-2.63)	2.07 (1.79-2.40)	1.05 (0.80-1.38)	1.18 (0.97-1.44)	1.71 (1.32-2.22)	2.31 (1.63-3.26)	1.27 (1.11-1.44)	1.29 (1.05-1.59)	1.45 (1.07-1.96)	2.19 (1.87-2.56)
Males	628 (35.9)	1 (ref)	1.43 (1.11-1.84)	1.26 (1.00-1.59)	1.93 (1.57-2.37)	1.91 (1.05-3.44)	1.85 (1.48-2.31)	1.01 (0.51-1.69)	1.15 (0.88-1.52)	1.70 (1.17-2.47)	1.65 (0.91-3.00)	1.29 (1.06-1.57)	1.76 (1.27-2.45)	1.38 (0.91-2.09)	2.04 (1.32-3.14)
Females	1137 (57.7)	1 (ref)	1.00 (0.82-1.24)	1.02 (0.79-1.31)	2.08 (1.73-2.50)	1.52 (1.02-2.27)	2.12 (1.72-2.60)	1.01 (0.72-1.43)	0.93 (0.70-1.26)	1.83 (1.25-2.69)	2.25 (1.44-3.52)	1.09 (0.91-1.30)	0.93 (0.71-1.23)	1.79 (1.12-2.85)	1.47 (1.22-1.77)
Substance abuse/ dependence[5]															
All	576 (15.5)	1 (ref)	0.77 (0.61-0.96)	0.89 (0.71-1.12)	2.10 (1.62-2.72)	1.22 (0.81-1.84)	1.82 (1.51-2.19)	0.89 (0.56-1.40)	0.90 (0.69-1.17)	1.55 (1.13-2.12)	1.26 (0.83-1.92)	0.97 (0.81-1.16)	1.17 (0.89-1.54)	1.42 (0.98-2.06)	0.78 (0.61-0.98)
Males	429 (24.5)	1 (ref)	0.82 (0.62-1.09)	0.66 (0.51-0.87)	2.65 (1.87-3.75)	1.00 (0.50-1.98)	1.94 (1.52-2.47)	0.98 (0.59-1.62)	0.98 (0.73-1.33)	1.62 (1.09-2.41)	1.79 (0.96-3.35)	1.12 (0.90-1.40)	1.64 (1.15-2.33)	1.24 (0.78-1.97)	1.36 (0.84-2.18)
Females	147 (7.5)	1 (ref)	0.80 (0.53-1.21)	1.00 (0.63-1.59)	2.11 (1.35-3.29)	2.48 (1.46-4.24)	2.60 (1.85-3.65)	0.82 (0.41-1.65)	1.58 (0.82-3.06)	1.53 (0.86-2.74)	1.64 (0.88-3.07)	1.06 (0.75-1.48)	0.89 (0.52-1.53)	1.66 (0.84-3.28)	1.41 (1.01-1.98)

[1]Tics, attention deficit hyperactivity disorder, conduct disorder, oppositional defiant disorder; [2]Separation anxiety disorder, overanxious disorder, specific phobias (animals), social phobia; [3]Generalized anxiety disorder, panic, agoraphobia, specific phobias (excl. animals); [4]Major depression disorder, dysthymia, bipolar disorders; [5]Alcohol, cannabis, other illicit drugs abuse/dependence; [6]Overall figures; Ns relating to each subgroup of mental disorders: 382 (neurodevelopmental), 1110 (early anxiety), 386 (late anxiety), 1446 (mood), 349 (substances); OR's were based on subgroup specific information; [7]Interparental violence, fear of maltreatment by parents, growing up in a children's home, unhappy childhood; [8]Tonsillitis, scarlet fever, rheumatic fever. MMR: Measles/mumps/rubella; [9]cystitis, pyelitis, pyelonephritis, other nephritis, urethritis, prostatitis.

Table 2 Mental disorders regressed on infectious, atopic and inflammatory diseases, odds-ratios and 95%CI derived from logistic regression models

	Model 1 Neurodevelopmental disorders	Model 2 Early anxiety disorders	Model 3 Late anxiety disorders	Model 4 Mood disorders	Model 5 Substance abuse/ dependence
Sex	0.38 (0.27-0.52)	1.60 (1.33-1.94)	1.50 (1.19-1.87)	2.05 (1.74-2.41)	0.19 (0.14-0.24)
Education level					
Low	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Medium	0.91 (0.66-1.24)	1.24 (1.01-1.52)	1.11 (0.87-1.41)	0.86 (0.72-1.04)	1.19 (0.92-1.54)
High	1.10 (0.78-1.56)	1.08 (0.87-1.34)	1.07 (0.83-1.39)	0.88 (0.72-1.06)	1.27 (0.98-1.66)
Familial aggregation of CMD	1.55 (1.07-2.23)	2.54 (2.14-3.01)	1.75 (1.34-2.29)	1.77 (1.52-2.06)	2.12 (1.59-2.82)
Trauma below age of 10	1.43 (0.84-2.44)	1.07 (0.73-1.57)	1.12 (0.73-1.71)	1.11 (0.76-1.62)	1.36 (0.84-2.20)
Childhood adversities	2.74 (2.09-3.60)	1.51 (1.25-1.81)	1.89 (1.53-2.33)	1.87 (1.57-2.23)	1.81 (1.45-2.27)
Streptococcal infections	1.29 (0.79-2.10)	1.11 (0.80-1.55)	1.22 (0.84-1.78)	0.80 (0.59-1.10)	0.80 (0.51-1.25)
Mumps, measles, rubella	1.37 (0.91-2.06)	1.36 (1.04-1.77)	1.33 (0.97-1.83)	1.07 (0.86-1.34)	1.15 (0.85-1.54)
Peptic ulcer/gastritis	1.72 (1.11-2.68)	1.23 (0.89-1.71)	1.47 (1.03-2.11)	1.74 (1.27-2.39)	1.58 (1.09-2.29)
Irritable bowel syndrome	1.30 (0.71-2.36)	1.81 (1.24-2.64)	1.74 (1.15-2.62)	1.87 (1.26-2.79)	1.70 (1.06-2.73)
Atopic diseases	0.95 (0.73-1.25)	1.11 (0.94-1.31)	1.24 (1.01-1.51)	1.06 (0.91-1.24)	1.02 (0.83-1.26)
Acne	0.83 (0.53-1.30)	1.10 (0.85-1.43)	1.02 (0.74-1.39)	1.23 (0.97-1.57)	1.27 (0.92-1.76)
Psoriasis	1.22 (0.69-2.16)	1.45 (0.99-2.11)	1.05 (0.66-1.69)	1.59 (1.11-2.28)	1.41 (0.91-2.19)
Urinary tract infections	1.51 (1.06-2.14)	1.37 (1.12-1.67)	1.06 (0.83-1.35)	1.49 (1.22-1.80)	1.20 (0.88-1.64)

CMD: Common mental disorders.

Table 3 Mental disorders regressed on infectious, atopic and inflammatory diseases, odds-ratios and 95%CIs derived from logistic regression models with nested effects

		Model 1 Neurodevelopmental disorders	Model 2 Early anxiety disorders	Model 3 Late anxiety disorders	Model 4 Mood disorders	Model 5 Substance abuse/ dependence
Sex		0.41 (0.23-0.72)	0.79 (0.54-1.15)	1.08 (0.68-1.69)	1.56 (1.08-2.26)	0.34 (0.21-0.54)
Education level						
Low		1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Medium		1.09 (0.79-1.49)	0.79 (0.65-0.98)	0.89 (0.70-1.13)	1.15 (0.96-1.38)	0.83 (0.64-1.08)
High		0.88 (0.62-1.25)	0.91 (0.73-1.14)	0.92 (0.71-1.20)	1.12 (0.92-1.36)	0.77 (0.59-1.01)
Familial aggregation of CMD		1.53 (1.06-2.21)	2.53 (2.14-3.00)	1.78 (1.36-2.33)	1.77 (1.52-2.06)	2.14 (1.60-2.86)
Trauma below age of 10		1.47 (0.86-2.50)	1.08 (0.73-1.58)	1.11 (0.73-1.71)	1.12 (0.76-1.64)	1.40 (0.86-2.27)
Childhood adversities		2.78 (2.12-3.65)	1.52 (1.26-1.83)	1.91 (1.55-2.36)	1.89 (1.59-2.25)	1.83 (1.46-2.29)
Streptococcal infections	Women nested	0.69 (0.29-1.67)	1.15 (0.76-1.73)	1.32 (0.84-2.07)	0.91 (0.60-1.36)	0.87 (0.42-1.82)
	Men nested	1.98 (1.08-3.66)	1.08 (0.60-1.92)	1.04 (0.51-2.09)	0.67 (0.40-1.12)	0.78 (0.44-1.39)
Mumps, measles, rubella	Women nested	1.16 (0.58-2.32)	1.46 (1.01-2.10)	1.81 (1.12-2.90)	0.97 (0.70-1.35)	1.62 (0.79-3.29)
	Men nested	1.47 (0.88-2.45)	1.29 (0.88-1.91)	0.96 (0.62-1.49)	1.12 (0.83-1.52)	1.04 (0.74-1.46)
Peptic ulcer/gastritis	Women nested	1.72 (0.88-3.34)	0.97 (0.63-1.49)	1.60 (1.02-2.51)	1.58 (1.02-2.46)	1.19 (0.61-2.35)
	Men nested	1.95 (1.08-3.53)	1.85 (1.13-3.05)	1.25 (0.67-2.35)	1.98 (1.26-3.09)	1.88 (1.18-2.99)
Irritable bowel syndrome	Women nested	1.23 (0.56-2.70)	1.48 (0.95-2.30)	1.60 (0.99-2.57)	2.25 (1.35-3.76)	1.63 (0.84-3.16)
	Men nested	1.74 (0.70-4.36)	3.15 (1.58-6.28)	1.97 (0.86-2.48)	1.33 (0.67-2.62)	1.80 (0.90-3.61)
Atopic diseases	Women nested	0.74 (0.48-1.12)	1.19 (0.96-1.47)	1.28 (0.99-1.66)	0.97 (0.79-1.18)	1.02 (0.69-1.49)
	Men nested	1.14 (0.80-1.61)	1.02 (0.77-1.34)	1.19 (0.86-1.66)	1.22 (0.97-1.53)	1.05 (0.81-1.35)
Acne	Women nested	0.75 (0.39-1.47)	0.94 (0.68-1.31)	0.82 (0.55-1.23)	0.90 (0.66-1.24)	0.74 (0.40-1.37)
	Men nested	0.92 (0.50-1.67)	1.47 (0.96-2.25)	1.52 (0.92-2.51)	1.96 (1.35-2.85)	1.74 (1.17-2.59)
Psoriasis	Women nested	0.84 (0.29-2.43)	1.05 (0.60-1.82)	1.48 (0.83-2.66)	2.02 (1.14-3.58)	1.70 (0.77-3.73)
	Men nested	1.44 (0.73-2.86)	2.02 (1.20-3.39)	0.60 (0.25-1.42)	1.33 (0.82-2.17)	1.30 (0.76-2.21)
Urinary tract infections	Women nested	1.68 (1.11-2.54)	1.44 (1.16-1.79)	0.94 (0.72-1.22)	1.47 (1.19-1.81)	1.30 (0.89-1.89)
	Men nested	1.26 (0.63-2.51)	0.99 (0.55-1.76)	2.13 (1.19-3.82)	1.63 (1.00-2.65)	1.04 (0.61-1.79)

CMD: Common mental disorders.

many associations were sex-specific. Intriguingly, accounting for interaction effects of infectious, atopic and inflammatory diseases with sex had different consequences for ND and CMD. In early and late anxiety disorders the sex main effect came down to one, meaning that the sex ratio in these disorders was fully determined by sex-specific associations with these risk factors.

Challenges

In view of the broad spectrum of results, the discussion will not focus on particular pathogens or findings as was done in the introduction, but will attempt to systematize them. Their interpretation encounters several basic challenges. First, the general heterogeneity of the associations between ND/CMD and infectious/atopic/ chronic inflammatory diseses is enormous. The extent

and heterogeneity of associations require appropriate, *i.e.*, neither universal nor parsimonious explanatory approaches. This methodological argument also applies also for the surprising sexual dimorphism of associations between ND/CMD and infectious, atopic and inflammatory diseases: There must be several mechanisms inducing sex-specific differences in rates of ND/CMD. Not least, this also applies to the different ages when CMD risk factors may emerge. While much attention has been paid to prenatal and perinatal events[76-78], the impact of MMR or scarlet fever in the current results shows that the age range can vary broadly. In brief: The same infectious disease or immune system imbalance could yield different vulnerability outcomes, depending on the age when it occurs.

Interpretation approaches

On a formal level the interpretation of the findings can follow three basic pathways (see, for example)[47]: (1) infectious, atopic and inflammatory diseases induce a risk for ND and CMD; (2) ND and CMD increase the risk for infectious, atopic and inflammatory diseases; and (3) both ND/CMD and infectious, atopic and inflammatory diseases share the same intermediate mechanisms or etiopathogenetic processes. These pathways will be used in the following to categorize and interpret the results.

Most of the current results point to the pathways one and three. In instances such as childhood infectious diseases the interpretation seems to be relatively unambiguous. Childhood infections lend themselves to the first pathway since they mostly precede other disorders or diseases. The range of potentially relevant pathogens, that figure as risk factors for mental disorders extends beyond well investigated prenatal infections (in the first place those summarized under the label TORCH - toxoplasmosis, rubella, cytomegalovirus, herpes)[79,80] and the PANDAS model (related to group A streptococcal infections in early childhood)[81]. In the current analysis it includes viral pathogens (MMR) in addition to streptococcal diseases. Moreover, the brief list of infectious diseases involved is to be understood as a preliminary compilation. More specific analyses, for example on anxiety disorders[82], would contribute additional links. In addition, several frequently occurring infectious agents in childhood cannot be adequately assessed by self-report data (*e.g.*, Haemophilus influenzae, respiratory syncytial virus, influenza).

Similar reasoning about the sequence of events also applies to atopic diseases. They often start in childhood and adolescence, *i.e.*, mostly before mood disorders (men) and late anxiety disorders (women). Thus, atopic diseases also seem to contribute to CMD rather than the other way round. However, atopic diseases represent a different type of immune system imbalance than infectious childhood diseases. It is a puzzling finding that the same disorder can be associated with risk factors which represent different, partly even antagonistic or competing immune system responses, such as Th1 *vs* Th2 or Th17 *vs* Treg[83].

This phenomenon can be perceived in associations related to chronic inflammatory diseases which represent pathway 3 above. For example, acne[84] and psoriasis[85] are assumed to be Th1/17 related skin diseases, whereas atopic eczema or the irritable bowel syndrome[57] are considered to have mainly[86] a Th2 related background.

Pathways 1 and 3 suggest that immunological processes are the common denominator of the related risk factors of ND/CMD. The immunological hypothesis in ND and CMD has many direct contributors, such as the TORCH (Toxoplasma gondii, rubella virus, cytomegalovirus, and herpes simplex virus)[80] and PANDAS models in ND disorders, serological studies, for example in schizophrenia (see above), leucocyte counts in depression[87], gastrointestinal inflammation in psychosis[29], the autoantibodies link[88], the inflammation topic in mood disorders[89], and, finally, evidence for upregulated proinflammatory mediators such as IL-1β, IL-6 and TNF-α[90]. However, in some instances such as UTI or ulcer the categorization of immune processes is less clear and may involve different basic mechanisms.

Hypotheses regarding the neurophysiological background mechanisms

The basic assumption of the immunological hypothesis within a two or three hit model (*i.e.*, a vulnerability-trigger model) of CMD is that immune system imbalances impact brain development during critical stages. Animal models referring to neonates have shown that bacterial infections may have an impact both on brain development and on the programming of the immune system[91-93]. While this research is based on *E. coli* models, the implications might generalize to other microbes, including streptococci, as well. It has been suggested that this pathway relies on the impact of cytokines on microglia, which in turn crucially influence brain development at different stages of life by influencing cell proliferation, synaptogenesis and immune processes in exchange with astrocytes, neurons and oligodendroglia[94,95]. An interesting perspective that has emerged recently is that mast cells are able to activate microglia[96].

In agreement with epidemiological research, the microglia pathway offers new perspectives for the understanding of the sex-ratios in mental disorders. Microglia numbers in males and females are differently skewed at different age stages. In early childhood, more microglia can be discerned in various brain regions of males, whereas in adolescence and adulthood, there are more microglia in the brains of females[97]. If more frequent, microglia are at the same time more "active"[94].

Limitations

While the promise of this study relies on a comprehensive epidemiological approach not feasible in most other subdisciplines in psychiatry, the study also has several limitations. First, all information is based on

the self-reporting of study subjects, which implies a substantial recall bias, both regarding mental problems and infectious diseases. Provided that infectious diseases remain asymptomatic in many instances and that underreporting is the most probable biasing effect regarding adverse experiences and stigmatized issues, our results represent rather conservative approximations of the "real" associations. Second, herpes as well as measles, mumps and rubella infections were presumably reported more frequently by subjects with a more severe or an exanthematic appearance of the infection. Thus, while these infections were underreported in this study, their frequencies implicitly provide a measure of disease severity. A similar limitation also applies to UTI and streptococcal infections. Third, the age of onset in streptococcal infections, herpes infections and in UTI could not be reliably assessed, the first two because of the inclusion of related diseases and late sequels, the latter because of the large proportion of undiagnosed or asymptomatic UTI in childhood. Finally, several further infectious agents of interest could not be identified by self report (see above) and thus could not be considered for the analysis.

In conclusion, atopic and inflammatory diseases make up an important group of potential risk factors for ND and CMD. They contribute independently of further major risk factors such as childhood adversities, traumatic experiences and familial aggregation. While the amount of evidence is enormous and continuously growing, the interpretational framework is compromised by the fact, that - similarly to research on smoking and cancer - direct experimental proofs are not feasible. Meanwhile, prevention in this field might already be going on unnoticed due to classical tools such as vaccinations and appropriate treatment of infectious diseases in childhood[98].

COMMENTS

Background

There are numerous results in the literature documenting the associations between inflammatory diseases of any kind (including infectious and atopic diseases) and neurodevelopmental disorders (ND)/common mental disorders (CMD). They complement other groups of risk factors (psychosocial stressors, traumatic experiences, pre-/perinatal risk factors, hormonal processes, substances, cerebral injury).

Research frontiers

In contrast to detailed knowledge about bivariate associations and particular issues, a systemic understanding is missing: How do these associations aggregate to more general mechanisms, how do they interact and compete? A better systemic understanding of the links between inflammatory diseases and ND/CMD might help us to understand even unresolved issues such as the sex ratios or the heterogeneous age at onset in these disorders.

Innovations and breakthroughs

This is the first study to apply a comprehensive epidemiological perspective on the associations of inflammatory diseases with major groups of ND and CMD while adjusting for other groups of risk factors. It confirms that inflammatory diseases make up an important group of risk factors of ND and CMD. However, the pathways are heterogeneous and sex-specific.

Applications

Inflammatory diseases are indicators of upregulations and imbalances in immune system activity. Since the immune system activity can be modulated and infectious diseases can be prevented, new potentials for intervention and prevention become apparent.

Terminology

Th1, Th2, Th17 are T helper cells, Treg are regulatory T cells. They represent different modes of immune system activity.

Peer-review

This is a very interesting body of work as a part on renewed interest in inflammatory processes and major psychiatric diseases.

REFERENCES

1 **Katz BZ**, Jason LA. Chronic fatigue syndrome following infections in adolescents. *Curr Opin Pediatr* 2013; **25**: 95-102 [PMID: 23263024 DOI: 10.1097/MOP.0b013e32835c1108]

2 **Wang X**, Zhang L, Lei Y, Liu X, Zhou X, Liu Y, Wang M, Yang L, Zhang L, Fan S, Xie P. Meta-analysis of infectious agents and depression. *Sci Rep* 2014; **4**: 4530 [PMID: 24681753 DOI: 10.1038/srep04530]

3 **Chen MH**, Wei HT, Su TP, Li CT, Lin WC, Chang WH, Chen TJ, Bai YM. Risk of depressive disorder among patients with herpes zoster: a nationwide population-based prospective study. *Psychosom Med* 2014; **76**: 285-291 [PMID: 24804885 DOI: 10.1097/PSY.0000000000000051]

4 **Liao CH**, Chang CS, Muo CH, Kao CH. High prevalence of herpes zoster in patients with depression. *J Clin Psychiatry* 2015; **76**: e1099-e1104 [PMID: 26455673 DOI: 10.4088/JCP.14m09311]

5 **Seminog OO**, Goldacre MJ. Risk of pneumonia and pneumococcal disease in people with severe mental illness: English record linkage studies. *Thorax* 2013; **68**: 171-176 [PMID: 23242947 DOI: 10.1136/thoraxjnl-2012-202480]

6 **Adam Y**, Meinlschmidt G, Lieb R. Associations between mental disorders and the common cold in adults: a population-based cross-sectional study. *J Psychosom Res* 2013; **74**: 69-73 [PMID: 23272991 DOI: 10.1016/j.jpsychores.2012.08.013]

7 **Martino D**, Defazio G, Giovannoni G. The PANDAS subgroup of tic disorders and childhood-onset obsessive-compulsive disorder. *J Psychosom Res* 2009; **67**: 547-557 [PMID: 19913659 DOI: 10.1016/j.jpsychores.2009.07.004]

8 **Murphy TK**, Storch EA, Lewin AB, Edge PJ, Goodman WK. Clinical factors associated with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. *J Pediatr* 2012; **160**: 314-319 [PMID: 21868033 DOI: 10.1016/j.jpeds.2011.07.012]

9 **Kayser MS**, Dalmau J. Anti-NMDA receptor encephalitis, autoimmunity, and psychosis. *Schizophr Res* 2016; **176**: 36-40 [PMID: 25458857]

10 **Khandaker GM**, Stochl J, Zammit S, Lewis G, Jones PB. Childhood Epstein-Barr Virus infection and subsequent risk of psychotic experiences in adolescence: a population-based prospective serological study. *Schizophr Res* 2014; **158**: 19-24 [PMID: 25048425 DOI: 10.1016/j.schres.2014.05.019]

11 **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 [PMID: 22103993 DOI: 10.1186/1471-2458-11-878]

12 **Goodwin RD**, Buka SL. Childhood respiratory disease and the risk of anxiety disorder and major depression in adulthood. *Arch Pediatr Adolesc Med* 2008; **162**: 774-780 [PMID: 18678811 DOI: 10.1001/archpedi.162.8.774]

13 **Nielsen PR**, Benros ME, Mortensen PB. Hospital contacts with infection and risk of schizophrenia: a population-based cohort study with linkage of Danish national registers. *Schizophr Bull* 2014; **40**: 1526-1532 [PMID: 24379444 DOI: 10.1093/schbul/sbt200]

14 **Yolken RH**, Torrey EF. Are some cases of psychosis caused by

microbial agents? A review of the evidence. *Mol Psychiatry* 2008; **13**: 470-479 [PMID: 18268502 DOI: 10.1038/mp.2008.5]
15 **Niebuhr DW**, Millikan AM, Cowan DN, Yolken R, Li Y, Weber NS. Selected infectious agents and risk of schizophrenia among U.S. military personnel. *Am J Psychiatry* 2008; **165**: 99-106 [PMID: 18086751 DOI: 10.1176/appi.ajp.2007.06081254]
16 **Yolken RH**, Torrey EF, Lieberman JA, Yang S, Dickerson FB. Serological evidence of exposure to Herpes Simplex Virus type 1 is associated with cognitive deficits in the CATIE schizophrenia sample. *Schizophr Res* 2011; **128**: 61-65 [PMID: 21353483 DOI: 10.1016/j.schres.2011.01.020]
17 **Schretlen DJ**, Vannorsdall TD, Winicki JM, Mushtaq Y, Hikida T, Sawa A, Yolken RH, Dickerson FB, Cascella NG. Neuroanatomic and cognitive abnormalities related to herpes simplex virus type 1 in schizophrenia. *Schizophr Res* 2010; **118**: 224-231 [PMID: 20153952 DOI: 10.1016/j.schres.2010.01.008]
18 **Wang H**, Yolken RH, Hoekstra PJ, Burger H, Klein HC. Antibodies to infectious agents and the positive symptom dimension of subclinical psychosis: The TRAILS study. *Schizophr Res* 2011; **129**: 47-51 [PMID: 21458236 DOI: 10.1016/j.schres.2011.03.013]
19 **Yolken RH**, Dickerson FB, Fuller Torrey E. Toxoplasma and schizophrenia. *Parasite Immunol* 2009; **31**: 706-715 [PMID: 19825110 DOI: 10.1111/j.1365-3024.2009.01131.x]
20 **Torrey EF**, Bartko JJ, Yolken RH. Toxoplasma gondii and other risk factors for schizophrenia: an update. *Schizophr Bull* 2012; **38**: 642-647 [PMID: 22446566 DOI: 10.1093/schbul/sbs043]
21 **Amminger GP**, McGorry PD, Berger GE, Wade D, Yung AR, Phillips LJ, Harrigan SM, Francey SM, Yolken RH. Antibodies to infectious agents in individuals at ultra-high risk for psychosis. *Biol Psychiatry* 2007; **61**: 1215-1217 [PMID: 17207471 DOI: 10.1016/j.biopsych.2006.09.034]
22 **Pedersen MG**, Stevens H, Pedersen CB, Nørgaard-Pedersen B, Mortensen PB. Toxoplasma infection and later development of schizophrenia in mothers. *Am J Psychiatry* 2011; **168**: 814-821 [PMID: 21536690 DOI: 10.1176/appi.ajp.2011.10091351]
23 **Park MH**, Kwon YJ, Jeong HY, Lee HY, Hwangbo Y, Yoon HJ, Shim SH. Association between Intracellular Infectious Agents and Schizophrenia. *Clin Psychopharmacol Neurosci* 2012; **10**: 117-123 [PMID: 23430959 DOI: 10.9758/cpn.2012.10.2.117]
24 **Krause D**, Matz J, Weidinger E, Wagner J, Wildenauer A, Obermeier M, Riedel M, Müller N. The association of infectious agents and schizophrenia. *World J Biol Psychiatry* 2010; **11**: 739-743 [PMID: 20602604 DOI: 10.3109/15622971003653246]
25 **Fellerhoff B**, Laumbacher B, Mueller N, Gu S, Wank R. Associations between Chlamydophila infections, schizophrenia and risk of HLA-A10. *Mol Psychiatry* 2007; **12**: 264-272 [PMID: 17102800 DOI: 10.1038/sj.mp.4001925]
26 **Fellerhoff B**, Laumbacher B, Wank R. High risk of schizophrenia and other mental disorders associated with chlamydial infections: hypothesis to combine drug treatment and adoptive immunotherapy. *Med Hypotheses* 2005; **65**: 243-252 [PMID: 15922095 DOI: 10.1016/j.mehy.2005.03.013]
27 **Banerjee B**, Petersen K. Psychosis following mycoplasma pneumonia. *Mil Med* 2009; **174**: 1001-1004 [PMID: 19780379]
28 **De Hert M**, Hautekeete M, De Wilde D, Peuskens J. High prevalence of Helicobacter pylori in institutionalized schizophrenic patients. *Schizophr Res* 1997; **26**: 243-244 [PMID: 9323357]
29 **Severance EG**, Alaedini A, Yang S, Halling M, Gressitt KL, Stallings CR, Origoni AE, Vaughan C, Khushalani S, Leweke FM, Dickerson FB, Yolken RH. Gastrointestinal inflammation and associated immune activation in schizophrenia. *Schizophr Res* 2012; **138**: 48-53 [PMID: 22446142 DOI: 10.1016/j.schres.2012.02.025]
30 **Linneberg A**, Ostergaard C, Tvede M, Andersen LP, Nielsen NH, Madsen F, Frølund L, Dirksen A, Jørgensen T. IgG antibodies against microorganisms and atopic disease in Danish adults: the Copenhagen Allergy Study. *J Allergy Clin Immunol* 2003; **111**: 847-853 [PMID: 12704368]
31 **Khandaker GM**, Zammit S, Lewis G, Jones PB. A population-based study of atopic disorders and inflammatory markers in childhood before psychotic experiences in adolescence. *Schizophr Res* 2014; **152**: 139-145 [PMID: 24268471 DOI: 10.1016/j.schres.2013.09.021]
32 **Cheng CM**, Hsu JW, Huang KL, Bai YM, Su TP, Li CT, Yang AC, Chang WH, Chen TJ, Tsai SJ, Chen MH. Risk of developing major depressive disorder and anxiety disorders among adolescents and adults with atopic dermatitis: a nationwide longitudinal study. *J Affect Disord* 2015; **178**: 60-65 [PMID: 25795537 DOI: 10.1016/j.jad.2015.02.025]
33 **Schmitt J**, Buske-Kirschbaum A, Roessner V. Is atopic disease a risk factor for attention-deficit/hyperactivity disorder? A systematic review. *Allergy* 2010; **65**: 1506-1524 [PMID: 20716320 DOI: 10.1111/j.1398-9995.2010.02449.x]
34 **Chen MH**, Wu YH, Su TP, Chen YS, Hsu JW, Huang KL, Li CT, Lin WC, Chang WH, Chen TJ, Bai YM. Risk of epilepsy among patients with atopic dermatitis: a nationwide longitudinal study. *Epilepsia* 2014; **55**: 1307-1312 [PMID: 24917387 DOI: 10.1111/epi.12667]
35 **Goodwin RD**, Sourander A, Duarte CS, Niemelä S, Multimäki P, Nikolakaros G, Helenius H, Piha J, Kumpulainen K, Moilanen I, Tamminen T, Almqvist F. Do mental health problems in childhood predict chronic physical conditions among males in early adulthood? Evidence from a community-based prospective study. *Psychol Med* 2009; **39**: 301-311 [PMID: 18507873 DOI: 10.1017/S0033291708003504]
36 **Alonso J**, de Jonge P, Lim CC, Aguilar-Gaxiola S, Bruffaerts R, Caldas-de-Almeida JM, Liu Z, O'Neill S, Stein DJ, Viana MC, Al-Hamzawi AO, Angermeyer MC, Borges G, Ciutan M, de Girolamo G, Fiestas F, Haro JM, Hu C, Kessler RC, Lépine JP, Levinson D, Nakamura Y, Posada-Villa J, Wojtyniak BJ, Scott KM. Association between mental disorders and subsequent adult onset asthma. *J Psychiatr Res* 2014; **59**: 179-188 [PMID: 25263276 DOI: 10.1016/j.jpsychires.2014.09.007]
37 **Goodwin RD**, Bandiera FC, Steinberg D, Ortega AN, Feldman JM. Asthma and mental health among youth: etiology, current knowledge and future directions. *Expert Rev Respir Med* 2012; **6**: 397-406 [PMID: 22971065 DOI: 10.1586/ers.12.34]
38 **Goodwin RD**, Fergusson DM, Horwood LJ. Asthma and depressive and anxiety disorders among young persons in the community. *Psychol Med* 2004; **34**: 1465-1474 [PMID: 15724877]
39 **Goodwin RD**, Fischer ME, Goldberg J. A twin study of post-traumatic stress disorder symptoms and asthma. *Am J Respir Crit Care Med* 2007; **176**: 983-987 [PMID: 17702964 DOI: 10.1164/rccm.200610-1467OC]
40 **Goodwin RD**, Pagura J, Cox B, Sareen J. Asthma and mental disorders in Canada: impact on functional impairment and mental health service use. *J Psychosom Res* 2010; **68**: 165-173 [PMID: 20105699 DOI: 10.1016/j.jpsychores.2009.06.005]
41 **Goodwin RD**, Robinson M, Sly PD, McKeague IW, Susser ES, Zubrick SR, Stanley FJ, Mattes E. Severity and persistence of asthma and mental health: a birth cohort study. *Psychol Med* 2013; **43**: 1313-1322 [PMID: 23171853 DOI: 10.1017/S0033291712001754]
42 **Hasler G**, Gergen PJ, Kleinbaum DG, Ajdacic V, Gamma A, Eich D, Rössler W, Angst J. Asthma and panic in young adults: a 20-year prospective community study. *Am J Respir Crit Care Med* 2005; **171**: 1224-1230 [PMID: 15764721]
43 **Scott KM**, Von Korff M, Ormel J, Zhang MY, Bruffaerts R, Alonso J, Kessler RC, Tachimori H, Karam E, Levinson D, Bromet EJ, Posada-Villa J, Gasquet I, Angermeyer MC, Borges G, de Girolamo G, Herman A, Haro JM. Mental disorders among adults with asthma: results from the World Mental Health Survey. *Gen Hosp Psychiatry* 2007; **29**: 123-133 [PMID: 17336661 DOI: 10.1016/j.genhosppsych.2006.12.006]
44 **Hak E**, de Vries TW, Hoekstra PJ, Jick SS. Association of childhood attention-deficit/hyperactivity disorder with atopic diseases and skin infections? A matched case-control study using the General Practice Research Database. *Ann Allergy Asthma Immunol* 2013; **111**: 102-106.e2 [PMID: 23886227 DOI: 10.1016/j.anai.2013.05.023]
45 **Goodwin RD**. Self-reported hay fever and panic attacks in the community. *Ann Allergy Asthma Immunol* 2002; **88**: 556-559 [PMID: 12086361 DOI: 10.1016/S1081-1206(10)61885-6]
46 **Sanna L**, Stuart AL, Pasco JA, Jacka FN, Berk M, Maes M, O'Neil A, Girardi P, Williams LJ. Atopic disorders and depression: findings from a large, population-based study. *J Affect Disord* 2014; **155**:

261-265 [PMID: 24308896 DOI: 10.1016/j.jad.2013.11.009]
47 **Buske-Kirschbaum A**, Schmitt J, Plessow F, Romanos M, Weidinger S, Roessner V. Psychoendocrine and psychoneuroimmunological mechanisms in the comorbidity of atopic eczema and attention deficit/hyperactivity disorder. *Psychoneuroendocrinology* 2013; **38**: 12-23 [PMID: 23141851 DOI: 10.1016/j.psyneuen.2012.09.017]
48 **Tsai JD**, Chang SN, Mou CH, Sung FC, Lue KH. Association between atopic diseases and attention-deficit/hyperactivity disorder in childhood: a population-based case-control study. *Ann Epidemiol* 2013; **23**: 185-188 [PMID: 23375343 DOI: 10.1016/j.annepidem.2012.12.015]
49 **Gupta MA**, Gupta AK, Vujcic B. Increased frequency of Attention Deficit Hyperactivity Disorder (ADHD) in acne versus dermatologic controls: analysis of an epidemiologic database from the US. *J Dermatolog Treat* 2014; **25**: 115-118 [PMID: 23030461 DOI: 10.3109/09546634.2012.736021]
50 **Bez Y**, Yesilova Y, Kaya MC, Sir A. High social phobia frequency and related disability in patients with acne vulgaris. *Eur J Dermatol* 2001; **21**: 756-760 [PMID: 21700535 DOI: 10.1684/ejd.2011.1418]
51 **Chen SJ**, Chao YL, Chen CY, Chang CM, Wu EC, Wu CS, Yeh HH, Chen CH, Tsai HJ. Prevalence of autoimmune diseases in in-patients with schizophrenia: nationwide population-based study. *Br J Psychiatry* 2012; **200**: 374-380 [PMID: 22442099 DOI: 10.1192/bjp.bp.111.092098]
52 **Spoendlin J**, Bichsel F, Voegel JJ, Jick SS, Meier CR. The association between psychiatric diseases, psychotropic drugs and the risk of incident rosacea. *Br J Dermatol* 2014; **170**: 878-883 [PMID: 24236423 DOI: 10.1111/bjd.12734]
53 **Goodwin RD**, Cowles RA, Galea S, Jacobi F. Gastritis and mental disorders. *J Psychiatr Res* 2013; **47**: 128-132 [PMID: 23073472 DOI: 10.1016/j.jpsychires.2012.09.016]
54 **Goodwin RD**, Talley NJ, Hotopf M, Cowles RA, Galea S, Jacobi F. A link between physician-diagnosed ulcer and anxiety disorders among adults. *Ann Epidemiol* 2013; **23**: 189-192 [PMID: 23453387 DOI: 10.1016/j.annepidem.2013.01.003]
55 **Goodwin RD**, Stein MB. Generalized anxiety disorder and peptic ulcer disease among adults in the United States. *Psychosom Med* 2002; **64**: 862-866 [PMID: 12461190]
56 **Goodwin RD**, Keyes KM, Stein MB, Talley NJ. Peptic ulcer and mental disorders among adults in the community: the role of nicotine and alcohol use disorders. *Psychosom Med* 2009; **71**: 463-468 [PMID: 19443694 DOI: 10.1097/PSY.0b013e3181988137]
57 **Tobin MC**, Moparty B, Farhadi A, DeMeo MT, Bansal PJ, Keshavarzian A. Atopic irritable bowel syndrome: a novel subgroup of irritable bowel syndrome with allergic manifestations. *Ann Allergy Asthma Immunol* 2008; **100**: 49-53 [PMID: 18254482 DOI: 10.1016/S1081-1206(10)60404-8]
58 **Roy-Byrne PP**, Davidson KW, Kessler RC, Asmundson GJ, Goodwin RD, Kubzansky L, Lydiard RB, Massie MJ, Katon W, Laden SK, Stein MB. Anxiety disorders and comorbid medical illness. *Gen Hosp Psychiatry* 2008; **30**: 208-225 [PMID: 18433653 DOI: 10.1016/j.genhosppsych.2007.12.006]
59 **Eaton WW**, Pedersen MG, Nielsen PR, Mortensen PB. Autoimmune diseases, bipolar disorder, and non-affective psychosis. *Bipolar Disord* 2010; **12**: 638-646 [PMID: 20868462 DOI: 10.1111/j.1399-5618.2010.00853.x]
60 **Chung KH**, Liu SP, Lin HC, Chung SD. Bladder pain syndrome/interstitial cystitis is associated with anxiety disorder. *Neurourol Urodyn* 2014; **33**: 101-105 [PMID: 24038135 DOI: 10.1002/nau.22382]
61 **Clemens JQ**, Elliott MN, Suttorp M, Berry SH. Temporal ordering of interstitial cystitis/bladder pain syndrome and non-bladder conditions. *Urology* 2012; **80**: 1227-1231 [PMID: 23206765 DOI: 10.1016/j.urology.2012.06.059]
62 **Miller BJ**, Graham KL, Bodenheimer CM, Culpepper NH, Waller JL, Buckley PF. A prevalence study of urinary tract infections in acute relapse of schizophrenia. *J Clin Psychiatry* 2013; **74**: 271-277 [PMID: 23561234 DOI: 10.4088/JCP.12m08050]
63 **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**: 1303-1310 [PMID: 22193673 DOI: 10.1176/appi.ajp.2011.11030516]
64 **Benito-León J**, Labiano-Fontcuberta A, Mitchell AJ, Moreno-García S, Martínez-Martín P. Multiple sclerosis is associated with high trait anger: a case-control study. *J Neurol Sci* 2014; **340**: 69-74 [PMID: 24635887 DOI: 10.1016/j.jns.2014.02.029]
65 **Feigenson KA**, Kusnecov AW, Silverstein SM. Inflammation and the two-hit hypothesis of schizophrenia. *Neurosci Biobehav Rev* 2014; **38**: 72-93 [PMID: 24247023 DOI: 10.1016/j.neubiorev.2013.11.006]
66 **Preisig M**, Waeber G, Vollenweider P, Bovet P, Rothen S, Vandeleur C, Guex P, Middleton L, Waterworth D, Mooser V, Tozzi F, Muglia P. The PsyCoLaus study: methodology and characteristics of the sample of a population-based survey on psychiatric disorders and their association with genetic and cardiovascular risk factors. *BMC Psychiatry* 2009; **9**: 9 [PMID: 19292899 DOI: 10.1186/1471-244X-9-9]
67 **Firmann M**, Mayor V, Vidal PM, Bochud M, Pécoud A, Hayoz D, Paccaud F, Preisig M, Song KS, Yuan X, Danoff TM, Stirnadel HA, Waterworth D, Mooser V, Waeber G, Vollenweider P. The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. *BMC Cardiovasc Disord* 2008; **8**: 6 [PMID: 18366642 DOI: 10.1186/1471-2261-8-6]
68 **Nurnberger JI**, Blehar MC, Kaufmann CA, York-Cooler C, Simpson SG, Harkavy-Friedman J, Severe JB, Malaspina D, Reich T. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH Genetics Initiative. *Arch Gen Psychiatry* 1994; **51**: 849-859; discussion 863-864 [PMID: 7944874]
69 **Preisig M**, Fenton BT, Matthey ML, Berney A, Ferrero F. Diagnostic interview for genetic studies (DIGS): inter-rater and test-retest reliability of the French version. *Eur Arch Psychiatry Clin Neurosci* 1999; **249**: 174-179 [PMID: 10449592]
70 **Berney A**, Preisig M, Matthey ML, Ferrero F, Fenton BT. Diagnostic interview for genetic studies (DIGS): inter-rater and test-retest reliability of alcohol and drug diagnoses. *Drug Alcohol Depend* 2002; **65**: 149-158 [PMID: 11772476]
71 **Endicott J**, Spitzer RL. A diagnostic interview: the schedule for affective disorders and schizophrenia. *Arch Gen Psychiatry* 1978; **35**: 837-844 [PMID: 678037]
72 **Leboyer M**, Maier W, Teherani M, Lichtermann D, D'Amato T, Franke P, Lépine JP, Minges J, McGuffin P. The reliability of the SADS-LA in a family study setting. *Eur Arch Psychiatry Clin Neurosci* 1991; **241**: 165-169 [PMID: 1790162]
73 **Ajdacic-Gross V**, Rodgers S, Müller M, Hengartner MP, Aleksandrowicz A, Kawohl W, Heekeren K, Rössler W, Angst J, Castelao E, Vandeleur C, Preisig M. Pure animal phobia is more specific than other specific phobias: epidemiological evidence from the Zurich Study, the ZInEP and the PsyCoLaus. *Eur Arch Psychiatry Clin Neurosci* 2016; **266**: 567-577 [PMID: 27001383 DOI: 10.1007/s00406-016-0687-4]
74 **Andreasen NC**, Endicott J, Spitzer RL, Winokur G. The family history method using diagnostic criteria. Reliability and validity. *Arch Gen Psychiatry* 1977; **34**: 1229-1235 [PMID: 911222]
75 **Rothen S**, Vandeleur CL, Lustenberger Y, Jeanprêtre N, Ayer E, Gamma F, Halfon O, Fornerod D, Ferrero F, Preisig M. Parent-child agreement and prevalence estimates of diagnoses in childhood: direct interview versus family history method. *Int J Methods Psychiatr Res* 2009; **18**: 96-109 [PMID: 19507167 DOI: 10.1002/mpr.281]
76 **Brown AS**, Derkits EJ. Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. *Am J Psychiatry* 2010; **167**: 261-280 [PMID: 20123911 DOI: 10.1176/appi.ajp.2009.09030361]
77 **Khandaker GM**, Zimbron J, Lewis G, Jones PB. Prenatal maternal infection, neurodevelopment and adult schizophrenia: a systematic review of population-based studies. *Psychol Med* 2013; **43**: 239-257 [PMID: 22717193 DOI: 10.1017/S0033291712000736]
78 **Meyer U**. Prenatal poly(i: C) exposure and other developmental immune activation models in rodent systems. *Biol Psychiatry* 2014; **75**: 307-315 [PMID: 23938317 DOI: 10.1016/j.biopsych.2013.07.011]
79 **Nickerson JP**, Richner B, Santy K, Lequin MH, Poretti A, Filippi CG, Huisman TA. Neuroimaging of pediatric intracranial infection--part 2:

TORCH, viral, fungal, and parasitic infections. *J Neuroimaging* 2012; **22**: e52-e63 [PMID: 22309611 DOI: 10.1111/j.1552-6569.2011.00699.x]

80 **Adams Waldorf KM**, McAdams RM. Influence of infection during pregnancy on fetal development. *Reproduction* 2013; **146**: R151-R162 [PMID: 23884862 DOI: 10.1530/REP-13-0232]

81 **Murphy TK**, Sajid MW, Goodman WK. Immunology of obsessive-compulsive disorder. *Psychiatr Clin North Am* 2006; **29**: 445-469 [PMID: 16650717 DOI: 10.1016/j.psc.2006.02.003]

82 **Witthauer C**, Gloster AT, Meyer AH, Goodwin RD, Lieb R. Comorbidity of infectious diseases and anxiety disorders in adults and its association with quality of life: a community study. *Front Public Health* 2014; **2**: 80 [PMID: 25072049 DOI: 10.3389/fpubh.2014.00080]

83 **Annunziato F**, Romagnani C, Romagnani S. The 3 major types of innate and adaptive cell-mediated effector immunity. *J Allergy Clin Immunol* 2015; **135**: 626-635 [PMID: 25528359 DOI: 10.1016/j.jaci.2014.11.001]

84 **Kistowska M**, Meier B, Proust T, Feldmeyer L, Cozzio A, Kuendig T, Contassot E, French LE. Propionibacterium acnes promotes Th17 and Th17/Th1 responses in acne patients. *J Invest Dermatol* 2015; **135**: 110-118 [PMID: 25010142 DOI: 10.1038/jid.2014.290]

85 **Diani M**, Altomare G, Reali E. T cell responses in psoriasis and psoriatic arthritis. *Autoimmun Rev* 2015; **14**: 286-292 [PMID: 25445403 DOI: 10.1016/j.autrev.2014.11.012]

86 **Eyerich K**, Novak N. Immunology of atopic eczema: overcoming the Th1/Th2 paradigm. *Allergy* 2013; **68**: 974-982 [PMID: 23889510 DOI: 10.1111/all.12184]

87 **Grosse L**, Hoogenboezem T, Ambrée O, Bellingrath S, Jörgens S, de Wit HJ, Wijkhuijs AM, Arolt V, Drexhage HA. Deficiencies of the T and natural killer cell system in major depressive disorder: T regulatory cell defects are associated with inflammatory monocyte activation. *Brain Behav Immun* 2016; **54**: 38-44 [PMID: 26674997 DOI: 10.1016/j.bbi.2015.12.003]

88 **Moscavitch SD**, Szyper-Kravitz M, Shoenfeld Y. Autoimmune pathology accounts for common manifestations in a wide range of neuro-psychiatric disorders: the olfactory and immune system interrelationship. *Clin Immunol* 2009; **130**: 235-243 [PMID: 19097945 DOI: 10.1016/j.clim.2008.10.010]

89 **Berk M**, Williams LJ, Jacka FN, O'Neil A, Pasco JA, Moylan S, Allen NB, Stuart AL, Hayley AC, Byrne ML, Maes M. So depression is an inflammatory disease, but where does the inflammation come from? *BMC Med* 2013; **11**: 200 [PMID: 24228900 DOI: 10.1186/1741-7015-11-200]

90 **Jones KA**, Thomsen C. The role of the innate immune system in psychiatric disorders. *Mol Cell Neurosci* 2013; **53**: 52-62 [PMID: 23064447 DOI: 10.1016/j.mcn.2012.10.002]

91 **Bilbo SD**, Schwarz JM. Early-life programming of later-life brain and behavior: a critical role for the immune system. *Front Behav Neurosci* 2009; **3**: 14 [PMID: 19738918 DOI: 10.3389/neuro.08.014.2009]

92 **Bilbo SD**, Schwarz JM. The immune system and developmental programming of brain and behavior. *Front Neuroendocrinol* 2012; **33**: 267-286 [PMID: 22982535 DOI: 10.1016/j.yfrne.2012.08.006]

93 **Lieblein-Boff JC**, McKim DB, Shea DT, Wei P, Deng Z, Sawicki C, Quan N, Bilbo SD, Bailey MT, McTigue DM, Godbout JP. Neonatal E. coli infection causes neuro-behavioral deficits associated with hypomyelination and neuronal sequestration of iron. *J Neurosci* 2013; **33**: 16334-16345 [PMID: 24107964 DOI: 10.1523/JNEUROSCI.0708-13.2013]

94 **Schwarz JM**, Bilbo SD. Sex, glia, and development: interactions in health and disease. *Horm Behav* 2012; **62**: 243-253 [PMID: 22387107 DOI: 10.1016/j.yhbeh.2012.02.018]

95 **Paolicelli RC**, Bolasco G, Pagani F, Maggi L, Scianni M, Panzanelli P, Giustetto M, Ferreira TA, Guiducci E, Dumas L, Ragozzino D, Gross CT. Synaptic pruning by microglia is necessary for normal brain development. *Science* 2011; **333**: 1456-1458 [PMID: 21778362 DOI: 10.1126/science.1202529]

96 **Zhang X**, Wang Y, Dong H, Xu Y, Zhang S. Induction of Microglial Activation by Mediators Released from Mast Cells. *Cell Physiol Biochem* 2016; **38**: 1520-1531 [PMID: 27050634 DOI: 10.1159/000443093]

97 **Schwarz JM**, Sholar PW, Bilbo SD. Sex differences in microglial colonization of the developing rat brain. *J Neurochem* 2012; **120**: 948-963 [PMID: 22182318 DOI: 10.1111/j.1471-4159.2011.07630.x]

98 **Ajdacic-Gross V**. The Prevention of Mental Disorders has a Bright Future. *Front Public Health* 2014; **2**: 60 [PMID: 24926477 DOI: 10.3389/fpubh.2014.00060]

P- Reviewer: Flyckt L, Müller MJ, Neto MLR **S- Editor**: Qiu S
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