Archival Report

Biological Psychiatry: Celebrating 50 Years

Parental Infections Before, During, and After Pregnancy as Risk Factors for Mental Disorders in Childhood and Adolescence: A Nationwide Danish Study

Cecilie N. Lydholm, Ole Köhler-Forsberg, Merete Nordentoft, Robert H. Yolken, Preben B. Mortensen, Liselotte Petersen, and Michael E. Benros

ABSTRACT

BACKGROUND: Previous studies have shown associations between maternal infections during pregnancy and increased risks of schizophrenia and autism spectrum disorder in the offspring. However, large-scale studies investigating an association between parental infections both during and outside the pregnancy period and the risk of any mental disorder in the child are lacking.

METHODS: A nationwide Danish cohort study identified 1,206,600 children born between 1996 and 2015 and followed them to a maximum of 20 years of age. Exposure included all maternal and paternal infections treated with anti-infective agents or hospital contacts before, during, or after pregnancy. The main outcome was a diagnosis of any mental disorder in the child. Hazard ratios (HRs) were calculated using Cox regression analysis.

RESULTS: Maternal infections during pregnancy treated with anti-infective agents (n = 567,016) increased the risk of mental disorders (n = 70,037) in the offspring (HR, 1.09; 95% confidence interval [CI], 1.06–1.12), which was more elevated ($p < .001$) than after paternal infections (n = 350,835; HR, 1.01; 95% CI, 0.98–1.03). Maternal hospital contacts for infections (n = 39,753) conferred an increased HR of 1.21 (95% CI, 1.14–1.28), which was not significantly (p = .08) different from the risk after paternal infections (n = 8559; HR, 1.07; 95% CI, 0.95–1.20). The increased risks observed during pregnancy were not different from the similarly increased risks for maternal and paternal infections before and after pregnancy. The risk of mental disorders increased in a dose-response relationship with the number of maternal infections treated with anti-infective agents, particularly during and after pregnancy (both $p < .001$).

CONCLUSIONS: Maternal infections were associated with an increased risk of mental disorder in the offspring; however, there were similar estimates during and outside the pregnancy period.

Keywords: Adolescent psychiatry, Child psychiatry, Inflammation, Parental infections, Pregnancy, Prenatal infections

https://doi.org/10.1016/j.biopsych.2018.09.013

Infections during pregnancy are common, and approximately 40% of all pregnant women in Denmark are exposed to infections treated with antibiotics during pregnancy (1). Over the last decades, maternal infections and inflammatory responses during pregnancy have increasingly been suggested to affect the fetal developing brain, elevating the risk of mental disorders in the offspring. The majority of studies have focused on psychosis and schizophrenia (2–16). Maternal infections during pregnancy with rubella (2), *Toxoplasma gondii* (3), herpes simplex virus type 2 (4,5), influenza virus (6,7), and bacterial infections during the first trimester (8) have been associated with an increased risk of schizophrenia in the offspring. However, the findings have not been consistent (3,9–11,17,18), and few epidemiological studies have investigated other mental disorders such as autism spectrum disorder (19–24) and affective disorder (3,25–29). Most prior studies have had several limitations, e.g., few cases (2,3,9), infections based on maternal self-report (12,20,21), or ecological study design (6,7). In the larger studies, exposure has mainly been based on infections requiring hospital contacts (11,13,19), thus disregarding the more commonly occurring infections treated by general practitioners. Finally, the majority of studies have not taken potentially important confounders into account, e.g., parental psychiatric diagnoses (8,21) or socioeconomic factors (3,13,19).

Several pathways have been suggested for the above-mentioned associations. Although the infection itself could impact the developing fetal central nervous system directly (2,3), it is also likely that maternal immune activation in response to infections plays a significant part (16,30,31), as similarly increased risks of mental disorders have been found across a wide range of infections and in relation to fever (12,20,21,32) and elevated acute phase reactants (23,33). Maternal immune activation is thought to influence the fetal

SEE COMMENTARY ON PAGE 285

ISSN: 0006-3223

microglia, which play a pivotal role in neural circuit formation and other neurodevelopmental processes (30). However, one previous study found that parental hospitalizations for infections before, during, and after pregnancy similarly increased the risk of schizophrenia (13). This has led to the question of whether the proposed relationship between infections and mental disorders is rather a shared genetic susceptibility to infections and mental disorders, which could also extend to other mental disorders. Furthermore, animal studies have investigated the intake of anti-infective medication during pregnancy and observed behavioral changes in the offspring, suggesting that alterations of the gut microbiome due to anti-infective medication are associated with behavioral changes in the absence of maternal infection (34–36).

We aimed to investigate the association between all treated parental infections during pregnancy in the primary and secondary care health sectors and the offspring's risk of being diagnosed with any mental disorder. We included a comparison of maternal and paternal infections during pregnancy with 40 weeks before and 40 weeks after the pregnancy period to examine if a possible association was confined to maternal infections during pregnancy or if it was merely a generally increased susceptibility to infections among the parents, as suggested by a previous study (13). Additionally, we investigated the risk of specific mental disorders, dose-response relationships, and associations with timing of infection exposure based on pregnancy trimester.

METHODS AND MATERIALS

Study Population

The present study is a nationwide, register-based cohort study covering the entire Danish population (approximately 5.5 million inhabitants). We included all children born in Denmark between July 1, 1996, and December 31, 2015, utilizing the Danish Civil Registration System (37). This register includes information on each resident in Denmark regarding place and date of birth, sex, and identity of parents, and assigns all Danish residents a unique personal identification number, which allows almost complete linkage between different registers. We excluded children with missing parental information establishing a cohort of 1,206,600 individuals. All individuals were followed from their first birthday to first outcome (see below), emigration, death, or end of the study period on April 22, 2017, whichever came first.

Exposure: Assessment of Infections

We identified all treated maternal and paternal infections via 1) prescribed anti-infective agents and 2) diagnosed infections requiring hospital contacts. Data on anti-infective agents were obtained through the National Prescription Registry (38), which contains information on all redeemed prescriptions since January 1, 1995. The anti-infective agents were divided into antibacterial agents and other anti-infective agents, i.e., antiviral, antimycotic, and antiparasitic (Supplemental Table S1). We decided a priori to group the viral, mycotic, and parasitic infections together (39), as we expected fewer cases in this group because the majority of these infections are not treated with anti-infective agents requiring prescription, or with medication at all. Infections requiring hospital contacts were identified via the National Patient Register (40), which has registered all diagnoses given in Danish somatic hospitals since 1977, including information on all outpatient contacts since January 1, 1995. Hospital contacts were divided into bacterial infections and other infections, i.e., viral, parasitic, and mycotic infections (Supplemental Table S2).

Exposure Periods

The abovementioned infections were identified before, during, and after the pregnancy period. We defined the pregnancy period as the 40 weeks before the date of birth. This period was subdivided into trimesters; weeks 0 to 12 (first trimester), weeks 13 to 28 (second trimester), weeks 29 to 40 (third trimester). The pre- and postpregnancy periods were defined as the 40 weeks before the pregnancy period and the 40 weeks following the date of birth, respectively.

Outcome: Assessment of Mental Disorders

The Danish Psychiatric Central Research Register (41) includes all hospitalizations in psychiatric hospitals since 1969 and outpatient treatment and emergency room contacts since January 1, 1995. We identified mental disorders within the cohort from first birthday to the end of study on April 22, 2017, both as inpatient admissions and as outpatient and psychiatric emergency department contacts. Our main outcome was any mental disorder defined as a diagnosis of F20 to F99 according to the ICD-10. We only included the main diagnosis of the first psychiatric hospital contact; hence, secondary diagnoses were not included. Our secondary outcomes were specific diagnoses depending on category according to ICD-10 (i.e., schizophrenia and schizotypal and delusional disorders [F20–29]; mood disorders [F30–39]; neurotic, stress-related, and somatoform disorders [F40–49]; behavioral syndromes associated with physiological disturbances and physical factors [F50–59]; disorders of adult personality and behavior [F60–69]; mental retardation [F70–79]; disorders of psychological development [F80–89]; and behavioral and emotional disorders with onset usually occurring in childhood and adolescence [F90–99]). Finally, we specifically identified autism spectrum disorder (ICD-10: F84.0, F84.1, F84.5, F84.8, F84.9). For specific diagnostic categories of mental disorders, we included the first psychiatric hospital contact with the diagnostic category in question.

Covariates

Sex and birth year were derived from the Danish Civil Registration System (37). Birth year was categorized into four groups (1996–2000, 2001–2005, 2006–2010, 2011–2015). Parental age at childbirth was categorized into five categories: <25 years of age, 25 to 29 years of age, 30 to 34 years of age, 35 to 39 years of age, and ≥ 40 years of age. Information on parental education was obtained from the Danish Education Registers (42) and was defined as the highest level of education at childbirth and divided into nine categories (primary education, upper secondary education, vocational education and training, qualifying educational programs, short-cycle higher education, vocational bachelor's education, bachelor's programs, master's education, Ph.D. programs). Parental psychiatric history

was defined as any diagnosis (ICD-10: F00–99; ICD-8: 290–315) before childbirth since 1969 (41). Parental physical illnesses was defined in accordance with the Charlson Comorbidity Index (43) modified for use with the ICD-10 (44) as a diagnosis of any of the 19 medical diseases considered in the Charlson Comorbidity Index before childbirth (40). The risk of spread of an infection from one parent to the other was handled by adjusting the analyses for concurrent infection (either treated with anti-infective agents or hospital contacts) in the other parent. Parental infection outside the time period was defined as one or more maternal or paternal infections in any other time periods.

Statistical Analyses

The primary analysis compared individuals who had been exposed to maternal infections treated with anti-infective agents or resulting in hospital contact before, during, or after the pregnancy period with nonexposed individuals during the specific period regarding the risk of any mental disorder. We performed the same analyses comparing individuals exposed to paternal infections with nonexposed individuals. In the secondary analysis, we investigated potential vulnerable periods for maternal or paternal infections during pregnancy depending on trimester. In the tertiary analysis, we investigated the risk of specific mental disorders by comparing individuals exposed to maternal or paternal infections before, during, or after the pregnancy period with nonexposed individuals during the specified periods. Furthermore, we investigated potential dose-response relationships between the number of infections treated with anti-infective agents and risk of mental disorders.

All analyses were performed with Stata version 13.1 (StataCorp, College Station, TX). We conducted Cox regression analyses with age as the underlying timescale and present results as hazard ratio (HR) with 95% confidence interval (CI). In all analyses, the underlying hazards were stratified by sex and adjusted for birth year, parental age at childbirth, parental educational level at childbirth, any parental psychiatric diagnoses before childbirth, parental physical illnesses before childbirth, concurrent infection in the other parent, and parental infections outside the time period. We adjusted for multiple comparisons using Bonferroni correction.

RESULTS

The cohort consisted of 1,206,600 children born July 1, 1996, to December 31, 2015, with 11.8 million person-years of follow-up from July 1, 1997, to April 22, 2017 (see Table 1 for characteristics of the study population). A total of 567,016 (47.0%) children were exposed to maternal infections treated with anti-infective agents during pregnancy, while 39,753 (3.3%) were exposed to maternal infections requiring hospital contacts during pregnancy (see Table 2 for all exposures before, during, and after pregnancy). A total of 70,037 (5.8%) individuals developed a mental disorder during the study period, of which 36,034 (51.5%) had been exposed to maternal infections treated with anti-infective agents during pregnancy and 2504 (3.6%) had been exposed to maternal infections requiring hospital contacts during pregnancy.

Table 1. Characteristics of Study Population at Time of Birth

	No Parental Infections During Pregnancy	≥1 Parental Infection During Pregnancy
Sex		
Male	238,198 (51.2)	380,583 (51.3)
Female	226,673 (48.8)	361,146 (48.7)
Maternal Age		
<25 years	54,827 (11.8)	101,531 (13.7)
25–29 years	159,636 (34.3)	244,553 (33.0)
30–34 years	167,666 (36.1)	262,505 (35.4)
35–39 years	70,691 (15.2)	113,478 (15.3)
≥40 years	12,051 (2.6)	19,662 (2.7)
Paternal Age		
<25 years	25,600 (5.5)	49,071 (6.6)
25–29 years	114,427 (24.6)	176,175 (23.8)
30–34 years	172,227 (37.1)	266,258 (35.9)
35–39 years	102,446 (22.0)	165,373 (22.3)
≥40 years	50,171 (10.8)	84,852 (11.4)
Maternal Level of Education		
Primary education	72,169 (15.5)	149,879 (20.2)
Upper secondary education	36,927 (7.9)	57,168 (7.7)
Vocational education and training	13,160 (2.8)	19,511 (2.6)
Qualifying educational programs	133,296 (28.7)	221,864 (29.9)
Short-cycle higher education	22,510 (4.8)	32,599 (4.4)
Vocational bachelors education	98,458 (21.2)	144,934 (19.5)
Bachelor's programs	14,916 (3.2)	19,226 (2.6)
Master's education	49,354 (10.6)	67,301 (9.1)
Ph.D. programs	1898 (0.4)	2367 (0.3)
Paternal Level of Education		
Primary education	78,086 (16.8)	151,424 (20.4)
Upper secondary education	25,779 (5.6)	38,980 (5.3)
Vocational education and training	11,518 (2.5)	17,306 (2.3)
Qualifying educational programs	175,327 (37.7)	288,869 (39.0)
Short-cycle higher education	29,297 (6.3)	42,952 (5.8)
Vocational bachelors education	53,578 (11.5)	78,558 (10.6)
Bachelors programs	11,719 (2.5)	15,307 (2.1)
Masters education	53,159 (11.4)	73,465 (9.9)
Ph.D. programs	3769 (0.8)	5021 (0.7)
Maternal Psychiatric Diagnosis		
No	440,598 (94.8)	685,837 (92.5)
Yes	24,273 (5.2)	55,892 (7.5)
Paternal Psychiatric Diagnosis		
No	449,094 (96.6)	707,410 (95.4)
Yes	15,777 (3.4)	34,319 (4.6)

Values are *n* (%).

Parental Infections During Pregnancy and the Risk of Mental Disorder in the Child

In the fully adjusted model, we found that children exposed to maternal infections treated with anti-infective agents during pregnancy had an increased risk of any mental disorder (HR, 1.09; 95% CI, 1.06–1.12) compared with children not exposed to maternal infections treated with anti-infective agents during pregnancy (Table 3). This was more elevated ($p < .001$) than

Table 2. Maternal and Paternal Infections Before, During, or After Pregnancy Among 1,206,600 Individuals

	Before Pregnancy	During Pregnancy	After Pregnancy
Maternal Infections			
Prescriptions	571,486 (47.4)	567,016 (47.0)	589,807 (48.9)
Bacterial	494,351 (41.0)	522,656 (43.3)	524,429 (43.5)
Other	194,717 (16.1)	116,687 (9.7)	176,977 (14.7)
Hospital contacts	15,338 (1.3)	39,753 (3.3)	34,599 (2.9)
Bacterial	9658 (0.8)	31,512 (2.6)	29,635 (2.5)
Other	6229 (0.5)	9809 (0.8)	6138 (0.5)
Paternal Infections			
Prescriptions	363,170 (30.1)	350,835 (29.1)	355,020 (29.4)
Bacterial	302,037 (25.0)	291,388 (24.2)	300,790 (24.9)
Other	102,233 (8.5)	98,181 (8.1)	91,692 (7.6)
Hospital contacts	8994 (0.8)	8559 (0.7)	9139 (0.8)
Bacterial	4462 (0.4)	4415 (0.4)	4670 (0.4)
Other	4861 (0.4)	4421 (0.4)	4833 (0.4)

Values are *n* (%). Numbers are based on one or more prescriptions for anti-infective agents or infections requiring hospital contact during the designated period.

after paternal infections treated with anti-infective agents during pregnancy (HR, 1.01; 95% CI, 0.98–1.03). Exposure to maternal infections requiring hospital contacts during pregnancy increased the risk of mental disorder (HR, 1.21; 95% CI, 1.14–1.28), which was not significantly ($p = .08$) different from the risk associated with paternal infections resulting in hospital contacts (HR, 1.07; 95% CI, 0.95–1.20). We found no difference in the increased risk of mental disorders after maternal infections of bacterial or other origin (Supplemental Table S3).

Regarding the site of the parental infection requiring hospital contact, only maternal sepsis conveyed an increased risk of mental disorders in the child (HR, 2.78; 95% CI, 1.16–6.67, $n = 8$) (Supplemental Table S4).

Parental Infections Before or After Pregnancy and the Risk of Mental Disorder in the Child

Most parental infections in the pre- or postpregnancy period showed increased risk estimates for any mental disorder similar to those of parental infections during pregnancy (Table 3). When performing Wald's test comparing the risk of mental disorders after maternal and paternal infections during the same time period, we found that the risks after maternal infections were significantly higher than after paternal infections for infections treated with anti-infective agents before, during, and after pregnancy (all $p < .03$), but found no significant difference between parental infections resulting in hospital contacts across all three periods. We found no interaction between sex of the offspring and risk of mental disorders after parental infections before, during, or after pregnancy.

Infections Based on Trimester and the Risk of Mental Disorder

We found an increased risk of mental disorders after maternal infections treated with anti-infective medication in the second and third trimesters and after maternal infections requiring hospital contacts in the third trimester, after correction for multiple comparisons (Table 4). The risk after maternal infections requiring hospital contacts in the third trimester was higher compared with before ($p = .04$) and after ($p = .04$) the pregnancy period. Paternal infections did not increase the risk of mental disorders in any trimester. We found no difference across trimesters in the increased risk depending on bacterial or other origin of maternal infection (Supplemental Table 5).

Risk of Specific Mental Disorders

There were no significantly increased risks of schizophrenia spectrum disorders (F20–29), mood disorders (F30–39), behavioral syndromes (F50–59), personality disorders (F60–69), or mental retardation (F70–79) in the analyses after correction for multiple comparisons (Table 5). We found an

Table 3. Risk of Any Mental Disorder in Offspring by Maternal and Paternal Infections Before, During, or After Pregnancy

	Prepregnancy Period		During Pregnancy		Postpregnancy Period	
	No. of Cases	Fully Adjusted HR (95% CI)	No. of Cases	Fully Adjusted HR (95% CI)	No. of Cases	Fully Adjusted HR (95% CI)
Maternal Infection Treated With Anti-infective Agents						
No infection	32,252	1.00 (ref)	34,003	1.00 (ref)	32,065	1.00 (ref)
≥1 infection	37,785	1.07 (1.05–1.10)[a]	36,034	1.09 (1.06–1.12)[a]	37,972	1.08 (1.05–1.11)[a]
Maternal Infection Requiring Hospital Contact						
No infection	68,951	1.00 (ref)	67,533	1.00 (ref)	67,967	1.00 (ref)
≥1 infection	1086	1.11 (1.02–1.21)	2504	1.21 (1.14–1.28)[a]	2070	1.13 (1.06–1.20)[a]
Paternal Infection Treated With Anti-infective Agents						
No infection	47,547	1.00 (ref)	48,181	1.00 (ref)	47,597	1.00 (ref)
≥1 infection	22,490	1.02 (1.00–1.05)	21,856	1.01 (0.98–1.03)	22,440	1.04 (1.01–1.06)
Paternal Infection Requiring Hospital Contact						
No infection	69,420	1.00 (ref)	69,460	1.00 (ref)	69,432	1.00 (ref)
≥1 infection	617	1.10 (0.98–1.24)	577	1.07 (0.95–1.20)	605	1.01 (0.90–1.14)

Hazard ratio (HR) and 95% confidence interval (CI) adjusted for sex, birth year, concurrent infection in the other parent, parental infections outside the time period, parental level of education at childbirth, parental age at childbirth, parental physical illnesses at childbirth, and any parental psychiatric diagnoses at childbirth (ICD-10: F00–99).

[a]Significant after correction for multiple comparisons.

Table 4. Risk of Any Mental Disorder in Offspring by Maternal and Paternal Infections During First, Second, and Third Trimesters of Pregnancy

	First Trimester		Second Trimester		Third Trimester	
	No. of Cases	Fully Adjusted HR (95% CI)	No. of Cases	Fully Adjusted HR (95% CI)	No. of Cases	Fully Adjusted HR (95% CI)
Maternal Infection Treated With Anti-infective Agents						
No infection	54,272	1.00 (ref)	52,780	1.00 (ref)	52,045	1.00 (ref)
≥1 infection	15,765	1.04 (1.01–1.07)	17,257	1.06 (1.03–1.09)[a]	17,992	1.09 (1.06–1.12)[a]
Maternal Infection Requiring Hospital Contact						
No infection	69,561	1.00 (ref)	69,225	1.00 (ref)	68,625	1.00 (ref)
≥1 infection	476	1.00 (0.87–1.14)	812	1.17 (1.05–1.29)	1412	1.25 (1.16–1.35)[a]
Paternal Infection Treated With Anti-infective Agents						
No infection	61,506	1.00 (ref)	60,528	1.00 (ref)	60,498	1.00 (ref)
≥1 infection	8531	1.02 (0.98–1.06)	9509	1.01 (0.98–1.05)	9539	1.00 (0.97–1.04)
Paternal Infection Requiring Hospital Contact						
No infection	69,869	1.00 (ref)	69,807	1.00 (ref)	69,813	1.00 (ref)
≥1 infection	168	1.01 (0.81–1.25)	230	1.11 (0.92–1.35)	224	1.17 (0.97–1.41)

Hazard ratio (HR) and 95% confidence interval (CI) adjusted for sex, birth year, concurrent infection in the other parent, parental infections outside the time period, parental level of education at childbirth, parental age at childbirth, parental physical illnesses at childbirth, and any parental psychiatric diagnoses at childbirth (ICD-10: F00–99).

[a]Significant after correction for multiple comparisons.

increased risk of anxiety disorders (F40–49) and of behavioral and emotional disorders (F90–99) after maternal infections before, during, and after pregnancy (Table 5). Maternal infections resulting in hospital contacts during and after pregnancy were associated with an increased risk of developmental disorders (F80–89), with HRs of 1.25 (95% CI, 1.13–1.40) and 1.23 (95% CI, 1.11–1.38), respectively. The estimates specifically for autism spectrum disorder after maternal infections requiring hospital contacts were similar, with an HR of 1.22 (95% CI, 1.08–1.37; $p = .001$) for infections during pregnancy and 1.20 (95% CI, 1.06–1.36; $p = .003$) for infections after pregnancy.

Dose-Response Associations

Figure 1 indicates that the risk for any mental disorder increased in a dose-response relationship depending on the number of maternal prescriptions during and after pregnancy (both $p < .001$). We found no dose-response associations with paternal prescriptions or the number of maternal or paternal hospital contacts.

DISCUSSION

Our nationwide study is the largest to date investigating the association between parental infections during pregnancy and risk of mental disorders in the offspring, covering all treated infections in the primary and secondary health care sector. We showed that maternal infections during pregnancy increased the risk of mental disorders in the child by 9% for infections treated with anti-infective agents and by 21% for infections requiring hospital contacts. Maternal infections during pregnancy displayed a higher risk than paternal infections regarding infections treated with anti-infective agents, whereas there was no significant difference for infections requiring hospital contact. However, the risk estimates after maternal infections outside the pregnancy period were similarly elevated compared with the risk after maternal infections during pregnancy. Maternal infections treated with anti-infective agents increased the risk, with a dose-response relationship both during pregnancy and after pregnancy, whereas no dose-response relationships were observed for paternal infections.

Previous studies have shown conflicting results (3,9–11,17,18), with some studies indicating that maternal infections during pregnancy could increase the risk of schizophrenia (2–8,13) and autism spectrum disorder (19,20,22–24) in particular; however, this is the first study to investigate the risk of any mental disorder in the offspring. Bacterial infections during the first trimester have been associated with schizophrenia (8), but a study by Nielsen *et al.* (13) found that the risk of schizophrenia in the child was similarly increased after maternal and paternal infections requiring hospital contacts before, during, or after pregnancy. In addition, Blomström *et al.* (11) found an increased risk of psychosis associated with maternal infections requiring hospitalization 5 years before pregnancy and with maternal infections during pregnancy for mothers with mental disorders. Regarding the risk of autism spectrum disorder, increased risks have been observed after viral infections during first trimester and bacterial infections during second trimester (19). Furthermore, Zerbo *et al.* (22) found that maternal infection diagnosed during hospitalization in the pregnancy period was associated with autism spectrum disorder, with an odds ratio of 1.48 (95% CI, 1.07–2.04). Our larger study found no increased risk of any mental disorder after maternal infections during the first trimester, but increased risks after maternal infections treated with anti-infective medication in the second and third trimesters and maternal infections requiring hospital contacts in the third trimester of pregnancy. We did not find a difference in the risk depending on bacterial or other origin of the infection. Although we also found similarly elevated risk estimates before, during, and after pregnancy, we found that maternal

Table 5. Risk of Specific Categories of Mental Disorders in Offspring After Exposure to Maternal or Paternal Infections Before, During, or After Pregnancy

	Schizophrenia Disorders (F20–29) (*n* = 2186)		Mood Disorders (F30–39) (*n* = 5559)		Anxiety Disorders (F40–49) (*n* = 18,453)		Behavioral Syndromes (F50–59) (*n* = 3302)		Personality Disorders (F60–69) (*n* = 1817)		Mental Retardation (F70–79) (*n* = 2843)		Developmental Disorders (F80–89) (*n* = 21,254)		Behavioral and Emotional Disorders (F90–99) (*n* = 33,005)	
	No. of Cases	Fully Adjusted HR (95% CI)	No. of Cases	Fully Adjusted HR (95% CI)	No. of Cases	Fully Adjusted HR (95% CI)	No. of Cases	Fully Adjusted HR (95% CI)	No. of Cases	Fully Adjusted HR (95% CI)	No. of Cases	Fully Adjusted HR (95% CI)	No. of Cases	Fully Adjusted HR (95% CI)	No. of Cases	Fully Adjusted HR (95% CI)
Before Pregnancy																
Maternal prescriptions	1214	0.92 (0.80–1.04)	3161	1.06 (0.98–1.15)	10,685	1.10 (1.05–1.15)[a]	1747	1.00 (0.89–1.11)	1105	1.09 (0.95–1.26)	1536	1.00 (0.89–1.13)	10,742	0.98 (0.94–1.03)	18,688	1.14 (1.10–1.19)[a]
Maternal hospital contacts	32	0.92 (0.57–1.48)	79	0.89 (0.65–1.22)	294	1.03 (0.88–1.22)	38	0.92 (0.60–1.41)	23	0.74 (0.43–1.29)	54	1.32 (0.92–1.90)	300	0.98 (0.83–1.16)	585	1.22 (1.09–1.38)
Paternal prescriptions	683	0.97 (0.85–1.11)	1859	1.04 (0.95–1.13)	6264	1.00 (0.95–1.05)	1061	1.12 (1.00–1.25)	626	1.07 (0.93–1.23)	871	0.95 (0.84–1.08)	6567	1.02 (0.98–1.07)	10,961	1.03 (0.99–1.07)
Paternal hospital contacts	18	1.08 (0.60–1.96)	56	1.31 (0.93–1.85)	183	1.24 (1.02–1.52)	24	0.96 (0.56–1.66)	19	1.22 (0.69–2.16)	24	1.11 (0.64–1.92)	188	1.18 (0.95–1.46)	310	1.06 (0.89–1.26)
During Pregnancy																
Maternal prescriptions	1151	1.14 (1.00–1.30)	2810	1.05 (0.97–1.14)	9906	1.09 (1.05–1.15)[a]	1621	1.12 (1.01–1.25)	941	0.99 (0.87–1.14)	1466	1.04 (0.93–1.17)	10,661	1.07 (1.03–1.12)	17,831	1.13 (1.09–1.17)[a]
Maternal hospital contacts	69	1.29 (0.95–1.77)	164	1.11 (0.90–1.38)	611	1.08 (0.96–1.21)	93	1.25 (0.95–1.66)	48	0.86 (0.58–1.28)	113	1.42 (1.10–1.84)	759	1.25 (1.12–1.38)[a]	1317	1.22 (1.12–1.33)[a]
Paternal prescriptions	709	1.10 (0.96–1.26)	1712	0.98 (0.90–1.07)	6035	1.02 (0.97–1.07)	970	0.95 (0.85–1.07)	575	1.03 (0.89–1.19)	913	0.94 (0.83–1.07)	6326	0.95 (0.91–1.00)	10,725	1.02 (0.98–1.06)
Paternal hospital contacts	19	0.93 (0.48–1.79)	40	0.92 (0.60–1.40)	162	1.08 (0.87–1.35)	28	1.49 (0.93–2.37)	15	1.18 (0.65–2.15)	20	1.20 (0.71–2.05)	157	1.12 (0.90–1.40)	318	1.13 (0.96–1.34)
After Pregnancy																
Maternal prescriptions	1244	1.08 (0.95–1.23)	3160	1.12 (1.04–1.22)	10,753	1.14 (1.09–1.19)[a]	1757	1.03 (0.92–1.14)	1092	1.18 (1.03–1.35)	1526	1.11 (0.98–1.25)	11,027	1.02 (0.97–1.06)	18,586	1.09 (1.06–1.14)[a]
Maternal hospital contacts	56	1.16 (0.83–1.62)	145	1.16 (0.93–1.43)	556	1.13 (1.00–1.27)	82	1.02 (0.75–1.39)	49	1.15 (0.80–1.64)	100	1.53 (1.18–1.99)	637	1.23 (1.11–1.38)[a]	1032	1.11 (1.01–1.22)
Paternal prescriptions	719	1.05 (0.92–1.20)	1844	1.12 (1.03–1.22)	6252	1.07 (1.02–1.12)	1019	1.03 (0.92–1.15)	599	1.12 (0.98–1.29)	921	1.03 (0.91–1.17)	6491	1.00 (0.96–1.05)	10,935	1.03 (0.99–1.07)
Paternal hospital contacts	19	0.84 (0.43–1.61)	52	1.04 (0.71–1.51)	167	0.91 (0.72–1.14)	22	0.94 (0.55–1.63)	18	0.89 (0.46–1.71)	25	1.12 (0.66–1.90)	174	1.11 (0.90–1.37)	312	1.04 (0.88–1.24)

Hazard ratio (HR) and 95% confidence interval (CI) adjusted for sex, birth year, concurrent infection in the other parent, parental level of education at childbirth, parental age at childbirth, parental physical illnesses at childbirth, and any parental psychiatric diagnoses at childbirth (ICD-10: F00–99). Reference value (HR, 1.00) is children with no maternal/paternal infection treated with anti-infective agents/requiring hospital contacts during the specified time period.

[a]$p < .001$ (significance level after correction for multiple comparisons).

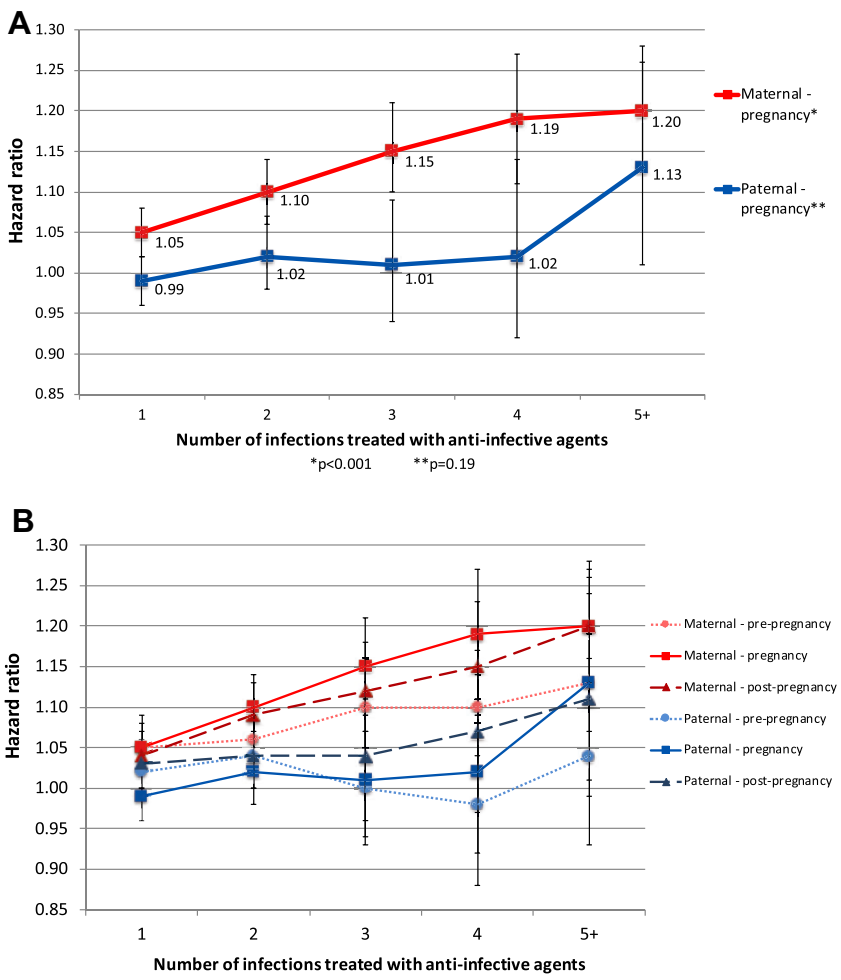

Figure 1. **(A)** Risk of any mental disorder in the child depending on the number of parental infections treated with anti-infective agents during pregnancy. **(B)** Risk of any mental disorder in the child depending on the number of parental infections treated with anti-infective agents before, during, or after pregnancy.

infections increased the risk of mental disorders more than paternal infections treated with anti-infective agents did.

Animal studies have suggested that the maternal immune response rather than specific infections drives the associations between maternal infections and increased risk of mental disorders in the offspring (16). However, our findings as well as those of others (11,13) suggest that the associations between parental infections and higher risks of mental disorders in the offspring not only are due to a possible effect of the infections, inflammation, or pregnancy complications as a result of infections, but also could partly be explained by shared genetic susceptibility to infections and mental disorders owing to the similar risk estimates after infections during and outside the pregnancy period. This is supported by findings from genetic studies with schizophrenia-associated genetic loci within areas coding for immune-related tissues (45), indicating immune dysregulation in schizophrenia (46). Still, prior studies have shown that the association between infections and schizophrenia does not seem to be affected by the common genes associated with schizophrenia (47). Nonetheless, shared genes with the susceptibility for acquiring infections not captured by the polygenic risk score for schizophrenia could still influence the association. However, it could also be an epiphenomenon due to reduced immunity of the parents with poor living conditions, psychological stress (48–50), lifestyle factors, medical-seeking behavior, or referral bias in which general practitioners may preferentially refer dysfunctional individuals to hospital treatment for serious infections. Nevertheless, shared familial confounding has been shown unlikely to explain the association between childhood infection and adult nonaffective psychosis (51). Moreover, all analyses were adjusted for parental level of education, parental psychiatric diagnoses, and chronic somatic diseases, capturing many important socioeconomic factors. Furthermore, our investigation did not look into specific infections that, during specific vulnerable periods, could potentially influence the fetal neurodevelopment. Last, recent animal studies have found associations between intake of anti-infective medication during pregnancy that could the maternal gut microbiome, and less exploratory behavior (34), reduced social interactions (35,36), and increased aggression in the offspring (36). This suggests that the mere intake of anti-infective medication could disturb the developing nervous system of the offspring, regardless of the presence of an infection, by altering the gut microbiota and influencing the gut-brain axis—a topic of great interest during recent years (52,53).

Strengths and Limitations

This study is a nationwide register-based cohort study with the advantages of complete follow-up and is not subject to recall bias. We had a large cohort yielding statistical power to investigate infections in specific vulnerable time periods, such as on a trimester basis. Furthermore, we were able to adjust for important confounders. The information on infections and mental disorders has high validity (38,40,41,54). All infections treated in the primary care sector as well as hospital contacts for infections were included. However, untreated infections could not be included. Hence, we cannot exclude the consequences of untreated infections, as most viruses such as influenza are only rarely treated with anti-infective medications. Furthermore, we were not able to separate the treatment from the infection itself, so it is possible that the risk of mental disorders is associated with the medication rather than the infection. However, we found similarly increased risks before, during, and after pregnancy, indicating that the use of anti-infective agents during pregnancy is as safe as the use outside the pregnancy period with regard to the future mental health of the child. Last, our cohort was fairly young, so the mental disorders were mainly within the spectrum of childhood and adolescent mental disorders, as the children were followed to a maximum age of 20 years. Hence, the estimates for the development of, for example, schizophrenia were based on a small subpopulation with early onset compared with the general population of individuals with schizophrenia and should therefore be interpreted with caution.

Conclusions and Perspectives

We found similarly increased risks of mental disorders in the offspring after exposure to maternal infections before, during, and after pregnancy—indicating that the pregnancy period was not a period of particular risk. The risk of mental disorders was generally higher for maternal infections and for infections resulting in hospital contact. For the pregnancy trimesters, increased risks were observed only during the second and third trimesters for infections treated with anti-infective agents and only in the third trimester for maternal infections requiring hospital contacts. Future studies need to investigate specific immune components during pregnancy together with shared genetic factors between infections and mental disorders.

ACKNOWLEDGMENTS AND DISCLOSURES

This study was supported by Independent Research Fund Denmark Grant No. 7025-00078B (to MEB), Lundbeck Foundation Grant No. R268-2016-3925 (to MEB), and an unrestricted scholarship grant from the Lundbeck Foundation (to CNL). The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Mental Health Centre Copenhagen (CNL, OK-F, MN, MEB), Faculty of Health Sciences, University of Copenhagen, Copenhagen; iPSYCH (CNL, OK-F, MN, PBM, LP, MEB), Lundbeck Foundation Initiative for Integrative Psychiatric Research; Psychosis Research Unit (OK-F), Aarhus University Hospital, Risskov; Department of Clinical Medicine (OK-F) and National Centre for Register-Based Research (PBM, LP, MEB), Aarhus University, Aarhus, Denmark; and Stanley Division of Neurovirology (RHY), Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland.

LP and MEB contributed equally to this work as joint last authors.

Address correspondence to Cecilie N. Lydholm, B.Sc., Mental Health Centre Copenhagen, Copenhagen University Hospital, Gentofte Hospital, Kildegaardsvej 28, Entrance 15, 4th Floor, 2900 Hellerup, Denmark; E-mail: rwt596@alumni.ku.dk.

Received Mar 13, 2018; revised Sep 5, 2018; accepted Sep 15, 2018.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2018.09.013.

REFERENCES

1. Broe A, Pottegård A, Lamont RF, Jørgensen JS, Damkier P (2014): Increasing use of antibiotics in pregnancy during the period 2000-2010: Prevalence, timing, category, and demographics. BJOG 121:988–996.
2. Brown AS (2000): Nonaffective psychosis after prenatal exposure to rubella. Am J Psychiatry 157:438–443.
3. Mortensen PB, Nørgaard-Pedersen B, Waltoft BL, Sørensen TL, Hougaard D, Torrey EF, *et al.* (2007): Toxoplasma gondii as a risk factor for early-onset schizophrenia: Analysis of filter paper blood samples obtained at birth. Biol Psychiatry 61:688–693.
4. Mortensen PB, Pedersen CB, Hougaard DM, Nørgaard-Petersen B, Mors O, Børglum AD, Yolken RH (2010): A Danish National Birth Cohort study of maternal HSV-2 antibodies as a risk factor for schizophrenia in their offspring. Schizophr Res 122:257–263.
5. Buka SL, Cannon TD, Torrey EF, Yolken RH; Collaborative Study Group on the Perinatal Origins of Severe Psychiatric Disorders (2008): Maternal exposure to herpes simplex virus and risk of psychosis among adult offspring. Biol Psychiatry 63:809–815.
6. O'Callaghan E, Sham P, Takei N, Murray RM, Glover G (1991): Schizophrenia after prenatal exposure to 1957 A2 influenza epidemic. Lancet 337:1248–1250.
7. McGrath JJ, Pemberton MR, Welham JL, Murray RM (1994): Schizophrenia and the influenza epidemics of 1954, 1957 and 1959: A southern hemisphere study. Schizophr Res 14:1–8.
8. Sørensen HJ, Mortensen EL, Reinisch JM, Mednick SA (2009): Association between prenatal exposure to bacterial infection and risk of Schizophrenia. Schizophr Bull 35:631–637.
9. Buka SL, Tsuang MT, Torrey EF, Klebanoff MA, Bernstein D, Yolken RH (2001): Maternal infections and subsequent psychosis among offspring. Arch Gen Psychiatry 58:1032–1037.
10. Blomström Å, Karlsson H, Wicks S, Yang S, Yolken RH, Dalman C (2012): Maternal antibodies to infectious agents and risk for non-affective psychoses in the offspring-a matched case-control study. Schizophr Res 140:25–30.
11. Blomström Å, Karlsson H, Gardner R, Jörgensen L, Magnusson C, Dalman C (2016): Associations between maternal infection during pregnancy, childhood infections, and the risk of subsequent psychotic disorder–A Swedish cohort study of nearly 2 million individuals. Schizophr Bull 42:125–133.
12. Dreier JW, Berg-Beckhoff G, Andersen AMN, Susser E, Nordentoft M, Strandberg-Larsen K (2018): Fever and infections during pregnancy and psychosis-like experiences in the offspring at age 11. A prospective study within the Danish National Birth Cohort. Psychol Med 48:426–436.
13. Nielsen PR, Laursen TM, Mortensen PB (2013): Association between parental hospital-treated infection and the risk of schizophrenia in adolescence and early adulthood. Schizophr Bull 39:230–237.
14. Khandaker GM, Zimbron J, Lewis G, Jones PB (2013): Prenatal maternal infection, neurodevelopment and adult schizophrenia: A systematic review of population-based studies. Psychol Med 43:239–257.
15. Flinkkilä E, Keski-Rahkonen A, Marttunen M, Raevuori A (2016): Prenatal inflammation, infections and mental disorders. Psychopathology 49:317–333.
16. Estes ML, Mcallister AK (2016): Maternal immune activation: Implications for neuropsychiatric disorders. Science 353:772–777.

17. Selten JP, Frissen A, Lensvelt-Mulders G, Morgan VA (2010): Schizophrenia and 1957 pandemic of influenza: Meta-analysis. Schizophr Bull 36:219–228.
18. Selten JP, Termorshuizen F (2017): The serological evidence for maternal influenza as risk factor for psychosis in offspring is insufficient: Critical review and meta-analysis. Schizophr Res 183:2–9.
19. Atladóttir HÓ, Thorsen P, Østergaard L, Schendel DE, Lemcke S, Abdallah M, *et al.* (2010): Maternal infection requiring hospitalization during pregnancy and autism spectrum disorders. J Autism Dev Disord 40:1423–1430.
20. Atladóttir HÓ, Henriksen TB, Schendel DE, Parner ET (2012): Autism after infection, febrile episodes, and antibiotic use during pregnancy: An exploratory study. Pediatrics 130:1447–1454.
21. Zerbo O, Iosif A-MM, Walker C, Ozonoff S, Hansen RL, Hertz-Picciotto I (2013): Is maternal influenza or fever during pregnancy associated with autism or developmental delays? Results from the CHARGE (childhood Autism Risks from Genetics and Environment) study. J Autism Dev Disord 43:25–33.
22. Zerbo O, Qian Y, Yoshida C, Grether JK, Van de Water J, Croen LA (2015): Maternal infection during pregnancy and autism spectrum disorders. J Autism Dev Disord 45:4015–4025.
23. Brown AS, Sourander A, Hinkka-Yli-Salomäki S, McKeague IW, Sundvall J, Surcel H-M (2013): Elevated maternal C-reactive protein and autism in a national birth cohort. Mol Psychiatry 19:259–264.
24. Fang S-Y, Wang S, Huang N, Yeh H-H, Chen C-Y (2015): Prenatal infection and autism spectrum disorders in childhood: A population-based case-control study in Taiwan. Paediatr Perinat Epidemiol 29:307–316.
25. Canetta SE, Bao Y, Co MDT, Ennis FA, Cruz J, Terajima M, *et al.* (2014): Serological documentation of maternal influenza exposure and bipolar disorder in adult offspring. Am J Psychiatry 171:557–563.
26. Mortensen PB, Pedersen CB, Mcgrath JJ, Hougaard DM, Nørgaard-Petersen B, Mors O, *et al.* (2011): Neonatal antibodies to infectious agents and risk of bipolar disorder: A population-based case-control study. Bipolar Disord 13:624–629.
27. Pang D, Syed S, Fine P, Jones PB (2009): No association between prenatal viral infection and depression in later life–A long-term cohort study of 6152 subjects. Can J Psychiatry 54:565–570.
28. Parboosing R, Bao Y, Shen L, Schaefer CA, Brown AS (2013): Gestational influenza and bipolar disorder in adult offspring. JAMA Psychiatry 70:677–685.
29. Simanek AM, Meier HCS (2015): Association between prenatal exposure to maternal infection and offspring mood disorders: A review of the literature. Curr Probl Pediatr Adolesc Health Care 45:325–364.
30. Knuesel I, Chicha L, Britschgi M, Schobel SA, Bodmer M, Hellings JA, *et al.* (2014): Maternal immune activation and abnormal brain development across CNS disorders. Nat Rev Neurol 10:643–660.
31. Patterson PH (2009): Immune involvement in schizophrenia and autism: Etiology, pathology and animal models. Behav Brain Res 204:313–321.
32. Werenberg Dreier J, Nybo Andersen A-M, Hvolby A, Garne E, Kragh Andersen P, Berg-Beckhoff G (2016): Fever and infections in pregnancy and risk of attention deficit/hyperactivity disorder in the offspring. J Child Psychol Psychiatry 57:540–548.
33. Canetta S, Sourander A, Surcel H-M, Hinkka-Yli-Salomäki S, Leiviskä J, Kellendonk C, *et al.* (2014): Elevated maternal C-reactive protein and increased risk of schizophrenia in a national birth cohort. Am J Psychiatry 171:960–968.
34. Tochitani S, Ikeno T, Ito T, Sakurai A, Yamauchi T, Matsuzaki H (2016): Administration of non-Absorbable antibiotics to pregnant mice to perturb the maternal gut microbiota is associated with alterations in offspring behavior. PLoS One 11:e0138293.
35. Degroote S, Hunting DJ, Baccarelli AA, Takser L (2016): Maternal gut and fetal brain connection: Increased anxiety and reduced social interactions in Wistar rat offspring following peri-conceptional antibiotic exposure. Prog Neuropsychopharmacol Biol Psychiatry 71: 76–82.
36. Leclercq S, Mian FM, Stanisz AM, Bindels LB, Cambier E, Ben-Amram H, *et al.* (2017): Low-dose penicillin in early life induces long-term changes in murine gut microbiota, brain cytokines and behavior. Nat Commun 8:15062.
37. Pedersen CB (2011): The Danish Civil Registration System. Scand J Public Health 39(7 suppl):22–25.
38. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M (2016): Data resource profile: The Danish National Prescription Registry. Int J Epidemiol 46:798–798f.
39. Köhler O, Petersen L, Mors O, Mortensen PB, Yolken RH, Gasse C, *et al.* (2017): Infections and exposure to anti-infective agents and the risk of severe mental disorders: A nationwide study. Acta Psychiatr Scand 135:97–105.
40. Lynge E, Sandegaard JL, Rebolj M (2011): The Danish National Patient Register. Scand J Public Health 39(7 suppl):30–33.
41. Mors O, Perto GP, Mortensen PB (2011): The Danish Psychiatric Central Research Register. Scand J Public Health 39(7 suppl):54–57.
42. Jensen VM, Rasmussen AW (2011): The Danish Education Registers. Scand J Public Health 39(7 suppl):91–94.
43. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987): A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 40:373–383.
44. Nuttall M, van der Meulen J, Emberton M (2006): Charlson scores based on ICD-10 administrative data were valid in assessing comorbidity in patients undergoing urological cancer surgery. J Clin Epidemiol 59:265–273.
45. Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014): Biological insights from 108 schizophrenia-associated genetic loci Nature 511:421–427.
46. Benros ME, Mortensen PB, Eaton WW (2012): Autoimmune diseases and infections as risk factors for schizophrenia. Ann N Y Acad Sci 1262:56–66.
47. Benros ME, Trabjerg BB, Meier S, Mattheisen M, Mortensen PB, Mors O, *et al.* (2016): Influence of polygenic risk scores on the association between infections and schizophrenia. Biol Psychiatry 80: 609–616.
48. Talge NM, Neal C, Glover V; Early Stress, Translational Research and Prevention Science Network: Fetal and Neonatal Experience on Child and Adolescent Mental Health (2007): Antenatal maternal stress and long-term effects on child neurodevelopment: How and why? J Child Psychol Psychiatry 48:245–261.
49. Varese F, Smeets F, Drukker M, Lieverse R, Lataster T, Viechtbauer W, *et al.* (2012): Childhood adversities increase the risk of psychosis: A meta-analysis of patient-control, prospective- and cross-sectional cohort studies. Schizophr Bull 38:661–671.
50. Matheson SL, Shepherd AM, Pinchbeck RM, Laurens KR, Carr VJ (2013): Childhood adversity in schizophrenia: A systematic meta-analysis. Psychol Med 43:225–238.
51. Khandaker GM, Dalman C, Kappelmann N, Stochl J, Dal H, Kosidou K, *et al.* (2018): Association of childhood infection with IQ and adult nonaffective psychosis in Swedish men a population-based longitudinal cohort and co-relative study. JAMA Psychiatry 75:356–362.
52. Foster JA, Lyte M, Meyer E, Cryan JF (2016): Gut microbiota and brain function: An evolving field in neuroscience. Int J Neuropsychopharmacol 19:pyv114.
53. Sharon G, Sampson TR, Geschwind DH, Mazmanian SK (2016): The central nervous system and the gut microbiome. Cell 167:915–932.
54. Uggerby P, Østergaard SD, Røge R, Correll CU, Nielsen J (2013): The validity of the schizophrenia diagnosis in the Danish Psychiatric Central Research Register is good. Dan Med J 60:A4578.