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Joint Effects of Exposure to Prenatal Infection and Peripubertal Psychological Trauma in Schizophrenia

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Context: **Prenatal infection and traumatizing experiences have both been linked with schizophrenia, but none of these factors seem sufficient to cause the disorder. However, recent evidence suggests that these environmental insults act in synergy to increase schizophrenia risk.** ***Objective:*** **To estimate the independent and joint effects of exposure to prenatal infection and peripubertal psychological trauma on the risk of schizophrenia.** ***Design:*** **Danish nationwide registers were linked in this prospective cohort study. We used survival analysis to report incidence rate ratios (IRRs) and corresponding 95% confidence intervals (95% CIs). Analyses were adjusted for age and calendar period and stratified by sex.** ***Participants:*** **A total of 979 701 persons born between 1980 and 1998 were followed up from January 1, 1995 through December 31, 2013, with 9656 having a hospital contact for schizophrenia.** ***Results:*** **Females exposed to prenatal infection had a significantly increased risk of schizophrenia (IRR: 1.61, 95% CI: 1.30–2.00), but not males (IRR: 0.99, 95% CI: 0.77–1.28). Peripubertal trauma was associated with increased risk in both sexes. Males, however, had a significantly higher risk of schizophrenia after exposure to both prenatal infection and peripubertal psychological trauma (IRR: 2.85, 95% CI: 2.32–3.51), with significant interaction between infection and peripubertal trauma on the multiplicative scale (*P* = .007).** ***Conclusions:*** **Our study demonstrated for the first time that prenatal infection and psychological trauma in peripubertal life can act in synergy to increase the risk of schizophrenia, with a potentially stronger susceptibility in males.**

Key words: schizophrenia/infections/peripubertal trauma/environment–environment interactions/epidemiology and nationwide registers

Introduction

Exposure to prenatal infection and traumatizing experiences during postnatal development are environmental insults that have both been linked with schizophrenia. More specifically, prenatal exposure to infection has been under extensive scrutiny, since Mednick et al[1] first reported an increased risk of schizophrenia among individuals prenatally exposed to the 1957 influenza epidemic in Helsinki. Even though replicated by many subsequent studies,[2,3] inconsistent findings have been reported as well.[4] Hence, the precise etiological role of prenatal influenza infection in schizophrenia remains elusive. It should also be noted, however, that influenza is not the only infectious agent that has been associated with schizophrenia. Other types of infections such as herpes,[5] toxoplasmosis,[6] and rubella[7] have also been implicated in this association. One prevalent hypothesis suggests that a common pathogenic mechanism involving increased production of cytokines and other mediators of inflammation mediates the link between prenatal infection and subsequent risk of schizophrenia.[8,9] Epidemiological support for this hypothesis, however, remains controversial,[10,11] suggesting furthermore that other mediating factors may play a role as well.[12]

Exposure to traumatizing events during postnatal development is another environmental insult that has received broad recognition in the etiology of neurodevelopmental disorders. Factors such as abuse, neglect, parental somatic illness and death, parental crime, divorce, and low socio-economic status, have all been associated with adverse mental health outcomes such as schizophrenia.[13–15] Although earlier much emphasis has been given to early exposure, time around puberty has recently emerged as a highly sensitive period to the

disruptive effects of environmental insults such as traumatizing experiences.[16–18]

Neither prenatal infection alone, nor exposure to traumatizing experiences alone, seems sufficient or necessary to cause schizophrenia. So far, most studies investigating these factors have estimated the relative effects of single exposures only, or in combination with genetic factors.[19,20]

A better understanding of the role these risk factors play in the etiology of schizophrenia necessitates efforts moving beyond analyses of single exposure only.

Recent animal studies have shown synergistic effects between prenatal immune activation and peripubertal stress, leading to morphological, neurochemical, and behavioral changes reminiscent of those frequently seen in psychotic illnesses.[21,22] Hence, in addition to gene–environment interactions, environment–environment interactions involving prenatal infection and peripubertal trauma may be involved in the etiology of schizophrenia and related psychotic disorders.

Although the translational aspects must be carefully addressed when translating results from animal models to the human condition, we believe it would expand our current knowledge if we test this hypothesis using one of the largest and most extensive register-databases worldwide. In light of the above, we sought to investigate joint effects between exposure to prenatal infection and traumatizing events in peripubertal life on the risk of developing schizophrenia. We hypothesized that (a) prenatal exposure to infection and peripubertal psychological trauma would both be associated with schizophrenia separately, but (b) when occurring jointly, they would interact to further increase the risk of schizophrenia. Given the relative differences in developmental timing, transient sex differences are likely to occur at certain time points during puberty.[17] Despite reports of emergent sex-differences in the adolescent brain,[23–25] there has been little emphasis on describing sex-specific changes in physiological responses to stressors during the period of puberty. Such changes could affect the risk of schizophrenia-relevant brain abnormalities, not only during adolescence but also for other developmental periods.[26] Consequently, we thought it relevant to take the sex specific risk of schizophrenia into account, when investigating exposures during developmental periods. We therefore (c) stratified the analysis by sex to take any effect modification into account.

It has been suggested that exposure early in *childhood* can be a proxy for more prolonged exposure or higher risk of exposure during adolescence.[18] To emphasize the effect of psychological trauma in the *peripubertal* period, we included the potentially confounding factor of *childhood* trauma in our analyses.

Materials and Methods

Study Design

We conducted a prospective cohort study on Danish register data, following 979 701 persons.

Participants

The cohort consisted of persons born in Denmark January 1, 1980 to December 31, 1998, by parents also born in Denmark, based on information from Danish nationwide registers.

The follow-up period started at the offspring's 15th birthday (ie, no earlier than January 1, 1995) and ended at the date of first recorded schizophrenia diagnosis after the age of 15, date of emigration, death, or December 31, 2013, whichever came first. Persons who emigrated, died or were diagnosed with schizophrenia spectrum disorder before age 15 were excluded.

Data Sources

Data were obtained by linking Danish nationwide population-based registers using the unique individual personal identification number, which is used across all national registers and allocated to all Danish citizens.

The Danish Civil Registration System (CRS) was established in 1968 and contains information on sex, date and place of birth, nationality, and the identification numbers of relatives among other information.[27] The Danish National Hospital Register (DNHR) was established in 1977 and includes information on all hospital admissions in Denmark. In 1994, it was expanded to also include emergency room and outpatient contacts.[28] The Danish Psychiatric Central Register includes all admission dates and diagnoses according to WHO ICD-8 and -10. It covers all psychiatric inpatient facilities in Denmark since 1969 and all outpatient contacts since 1994.[29]

Exposure

Prenatal Infection. A history of infection was defined as the mother of the offspring having been admitted with an infection during pregnancy. Infections were diagnosed according to WHO ICD-8 and -10 codes, and included viral, bacterial and other infections, described in detail in a previously published article.[30] Gestational age was unknown for 129 501 individuals (13.22%) and in those offspring assumed to be 280 days.

Psychological Trauma. We included exposure to traumatizing experiences during the period of peripuberty (from age 8 to 14 years) as defined according to Danish standards.[31] Psychological trauma was defined the following way:

Parental deaths. Maternal and Paternal Chronic Somatic Diseases Measured using Charlson Comorbidity Index. The first occurrence of a score greater than 0 (after excluding age from the index), using contacts (in- or outpatient) from The National Patient Register.

Social Paediatrics Contacts Any contact (in- or outpatient) in the DNHR with a diagnosis of maltreatment

or abuse. These variables are available from 1994 and onwards.

Foster Care First record of child being placed outside of home.

Family Composition First record of child not living with both legal parents (Statistics Denmark; The FAIN dataset [households and families]).

Maternal and Paternal History of Crime A record of convictions after birth of offspring. Only custodial sentences regarding the criminal code, the weapons law and the law on narcotics and drunk driving were used.

Maternal and Paternal Occupational Situation First record of permanently leaving the workforce for each parent after the child is born.

Outcome

Cohort members were classified with schizophrenia (ICD-8: 295; ICD-10: F20), and schizophrenia-like psychoses, including schizophrenia-related personality disorders, schizoaffective disorder, delusional disorder, and schizophreniform disorder (ICD-8: 295.x9, 296.89, 297.x9, 298.29–298.99, 299.04, 299.05, 299.09, and 301.83; ICD-10: F20–F29) if the individual had been admitted to a psychiatric hospital or been in outpatient care with that diagnosis. Date of onset was defined as first day of first contact (in- or outpatient) with a schizophrenia spectrum diagnosis, irrespective of other previous psychiatric diagnoses.

Covariates

Based on the literature, the following variables were included as potential confounders: Parental diagnoses of schizophrenia spectrum disorder (as defined for cohort members) or any other psychiatric disorder.[32] Mother's and father's highest attained educational level the year prior to birth of the offspring (9, 10–12, and >12 years [reference]).[33]

To allow for variation in incidence of schizophrenia, all models were adjusted for calendar period in 5-year intervals from 1995 and onwards.

Statistical Analyses

Incidence rate ratios (IRRs) were estimated by Cox propotional hazards method in Stata Software 13.0 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.). Main exposure variables were exposure to prenatal infection and peripubertal psychological trauma. Analyses were adjusted for calendar period and age. Subsequent analyses were adjusted for family history of psychiatric disorders, parental educational level, and childhood psychological trauma. All analyses were repeated after stratification for sex.

Calendar period and psychiatric family history were treated as time-dependent covariates, with age as the underlying timescale.

To investigate synergistic effects of prenatal infection and peripubertal psychological trauma on the multiplicative scale, we included an interaction term between them in the proportional hazards model. In the model stratified by sex, we tested for interaction by including a 3-way interaction term, between prenatal infection, peripubertal psychological trauma and sex, while also including an interaction term between each of the covariates and sex.

IRRs and CIs were calculated by maximum likelihood estimation. *P* values and tests for differences were assessed using the Wald test.

Sensitivity Analyses

First, to explore the possible role of postnatal timing,[21] we included childhood psychological trauma (from birth to age 7 years) as an exposure while adjusting for peripubertal psychological trauma. We used the same variables as for peripubertal psychological trauma.

Second, analyses were repeated after stratification for family history of psychiatric disorders. Previous research has indicated that family history of psychosis might modify the association between prenatal infection and schizophrenia,[19,30,34] and we did this analysis to control more rigorously for this strong risk factor. We tested for interaction with psychiatric family history by including the 3-way interaction and an interaction term between each covariate and the strata variable, as was done for sex.

Approval

The Danish National Board of Health and the Danish Data Protection Agency approved the project.

Results

A total of 979 701 individuals were included in the cohort. Of these 9656 were diagnosed with a schizophrenia spectrum disorder within follow-up between January 1, 1995 and December 31, 2013. Baseline characteristics of the study sample are presented in table 1.

Independent and Combined Effects of Infection and Peripubertal Psychological Trauma

Table 2 presents the hazard ratios (HRs) of schizophrenia spectrum disorder after exposure to prenatal infection, peripubertal psychological trauma, and both, with the groups being mutually exclusive. Offspring exposed to prenatal infection had a 1.28-fold (95% confidence interval [CI]: 1.08–1.51) increased risk of schizophrenia. Peripubertal psychological trauma was associated with a risk of 1.75 (95% CI: 1.68–1.83), whereas exposure to both insults led to a 2.51-fold (95% CI: 2.14–2.95) increased risk of schizophrenia compared to the reference group. Exposure to both was associated with a significantly higher risk compared to exposure to

Table 1. Baseline Characteristics of the Study Sample (n = 979 701)

	Diagnosis of Schizophrenia Spectrum disorder (n = 9656, 0.99%)		No Diagnosis of Schizophrenia Spectrum Disorder (n = 970 045, 99.1%)	
	N	%	*n*	%
Male	5184	53.69	497 610	51.30
Parental psychiatric family history				
None	6954	72.02	823 582	84.90
Any psychiatry	2133	22.09	130 574	13.46
Schizophrenia spectrum disorder	569	5.89	15 889	1.64
Highest attained educational level (years)				
Mother				
9	4421	45.79	308 021	31.75
10–12	2871	29.73	388 830	40.08
>12	1513	15.67	215 004	22.16
Missing	851	8.81	58 190	6.00
Father				
9	3484	36.08	243 160	25.07
10–12	3934	40.74	476 008	49.07
>12	1314	13.61	185 750	19.15
Missing	924	9.57	65 127	6.71
Exposed to childhood psychological trauma	5060	52.40	339 484	35.00

Table 2. Incidence Rate Ratios of Schizophrenia Spectrum Disorder After Exposure to Prenatal Infection and Peripubertal Psychological Trauma in a Cohort of 979 701 Persons Born Between 1980 and 1998 of Whom 9656 Developed Schizophrenia

			IRRs (95% CI)	
Exposure Status	Cases	Incidence Rate[a]	Basic Model[b]	Adjusted Model[c]
No prenatal infection, no peripubertal psychological trauma	5687	0.90	1.00 (reference)	1.00 (reference)
Prenatal infection, no peripubertal psychological trauma	146	1.15	1.28 (1.09–1.51)	1.05 (0.88–1.25)
Peripubertal psychological trauma, no prenatal infection	3668	1.59	1.75 (1.68–1.83)	1.36 (1.30–1.42)
Prenatal infection and peripubertal psychological trauma	155	2.29	2.51 (2.14–2.95)	1.58 (1.33–1.88)

Note: IRR, incidence rate ratio.
[a]The incidence rate measures the number of new cases per 1000 person years.
[b]Adjusted for calendar period and age.
[c]Further adjusted for parental psychiatric family history, parental education, and *childhood* psychological trauma (from birth to 7 years of age).

either insult alone (test for difference; $P < .0001$ and $P < .0001$, respectively), although no significant interaction was found between prenatal infection and peripubertal psychological trauma on the multiplicative scale. Adjustment for family history of psychiatric disorders, parental education, and exposure to *childhood* psychological trauma attenuated the risk as expected, but exposure to peripubertal psychological trauma (IRR 1.36, 95% CI: 1.30–1.42) and exposure to both (IRR 1.58, 95% CI: 1.33–1.88) remained significantly associated with schizophrenia (table 2).

Effect Modification by Sex

In the model stratified by sex (table 3), females had a significantly higher (P = .007) risk of schizophrenia after exposure to prenatal infection only (IRR: 1.61, 95% CI: 1.30–2.00) compared to males (IRR: 0.99, 95% CI: 0.77–1.28). This was irrespective of adjustment for confounding factors.

Both sexes had a significantly increased risk of schizophrenia after exposure to peripubertal trauma only (IRR: 1.71, 95% CI: 1.60–1.81) and (IRR: 1.80, 95% CI: 1.70–1.90), for females and males, respectively.

Table 3. Sex Stratified Incidence Rate Ratios of Schizophrenia Spectrum Disorder After Exposure to Prenatal Infection and Peripubertal Psychological Trauma in a Cohort of 979 701 Persons Born Between 1980 and 1998 of Whom 9656 Developed Schizophrenia

	Female				Male			
			IRRs (95% CI)				IRRs (95% CI)	
Exposure Status	Cases	Incidence Rate[a]	Basic Model[b]	Adjusted Model[c]	Cases	Incidence Rate[a]	Basic Model[b]	Adjusted Model[c]
No prenatal infection, no peripubertal psychological trauma	2651	0.86	1.00 (reference)	1.00 (reference)	3036	0.94	1.00 (reference)	1.00 (reference)
Prenatal infection, no peripububertal psychological trauma	85	1.39	1.61 (1.30–2.00)	1.33 (1.05–1.67)	61	0.92	0.99 (0.77–1.28)	0.81 (0.62–1.07)
Peripubertal psychological trauma, no prenatal infection	1674	1.49	1.71 (1.60–1.81)	1.35 (1.26–1.44)	1994	1.69	1.80 (1.70–1.90)	1.37 (1.28–1.46)
Prenatal infection and peripubertal psychological trauma	62	1.86	2.13 (1.65–2.74)	1.33 (1.01–1.76)	93	2.69	2.85 (2.32–3.51)	1.80 (1.44–2.26)

Note: CI, confidence interval; IRR, incidence rate ratio.
[a]The incidence rate measures the number of new cases per 1000 person years.
[b]Adjusted for calendar period and age.
[c]Further adjusted for parental psychiatric family history, parental education and *childhood* psychological trauma (from birth to 7 years of age).

Males first exposed to infection and subsequently exposed to peripubertal psychological trauma (IRR: 2.85, 95% CI: 2.32–3.51), had a significantly higher risk compared to their male counterparts exposed to prenatal infection only ($P < .0001$) or peripubertal psychological trauma only ($P = .0045$). Females exposed to both infection and peripubertal trauma did not have a higher risk compared to females exposed to prenatal infection only ($P = .97$) or peripubertal trauma only ($P = .94$). In males we found significant interaction between prenatal infection and peripubertal trauma on the multiplicative scale ($P = .007$). The 3-way interaction term between prenatal infection, peripubertal psychological trauma and sex, revealed significant difference of the interaction between males and females ($P = .003$), giving further evidence in support of synergistic effects of prenatal infection and peripubertal trauma in males. However, although significant interaction was found in males, no significant difference was observed between males and females exposed to both environmental insults ($P = .1$).

Sensitivity Analyses

Exposure to childhood psychological trauma was consistently associated with schizophrenia in both males and females as expected (data not shown). However, exposure to both prenatal infection and *childhood* psychological trauma was not associated with a significantly higher risk compared to exposure to either only, and we found no evidence for interaction on the multiplicative scale in the combined model (test for interaction; $P = .33$), or in the model stratified by sex.

In the analysis stratified by level of family history of psychiatric disorders we found no difference of effects between groups (supplementary figure 1). Furthermore, no interaction was found between either level of family history and exposure to either or both environmental insults.

A table of all single exposure variables with corresponding HRs and 95% confidence intervals (95% CI) are shown in supplementary table 1.

Discussion

Using one of the largest population databases currently available, we aimed to confirm the hypothesis put forward by recent preclinical animal studies suggesting that exposure to prenatal infection and traumatizing experiences in peripuberty act in synergy to increase the risk of schizophrenia-relevant brain abnormalities.[21] Our findings suggest that this may indeed be the case. We found that combined exposure to both insults was associated with significantly higher risk of developing schizophrenia as compared to exposure to either insult alone. The higher risk of schizophrenia observed after exposure to both prenatal infection and peripubertal trauma, was primarily due to significant interaction on the multiplicative scale between the 2 environmental insults in males. Test of the 3-way interaction between prenatal infection, peripubertal trauma, and sex, revealed significant higher interaction in males compared to females.

The association between prenatal infection and schizophrenia was modest, but similar in magnitude to what has been found in previous studies.[19,30] In the fully adjusted model, the association was no longer significant, in line with recently published results by Blomstrom et al.[34] However, sex was an effect modifier of this association, with a significantly increased risk of schizophrenia in females after prenatal exposure alone. Because the exposure groups were mutually exclusive, we do not expect association to occur because of confounding by peripubertal trauma, and the differences were also observed after adjustment for a family history of psychiatric disorder and exposure to childhood psychological trauma. Hence, females appear to be more sensitive than males with respect to the influences of prenatal infection. To the best of our knowledge, no other study has investigated sex differences in a similar setting. However, a word of caution is warranted in the interpretation of the results, because more males exposed to prenatal infection could go on to develop schizophrenia after the end of observation, which could reduce the sex differences.

In the landmark study by Mednick et al,[1] the authors found an increased risk of schizophrenia after prenatal exposure to influenza in the second trimester.[1] Although not consistently, other researchers have also pointed to a trimester specific effect and an effect specific to the infectious agent, as reviewed by Brown and Derkits.[35] Due to inadequate power, we did not stratify prenatal exposure to infection by trimester of exposure or infectious agent, and we cannot rule out the possibility that some types of infections may be more harmful to the fetus than others or that of a timing effect. Evidence from the recent population-based studies from Sweden and Denmark, however, did not support the notion of a trimester or agent specific effect.[30,34] Because there is a major overlap between the cohort in the present study and the one in the study by Nielsen et al,[30] we would expect much of the same effect regarding timing and agent of exposure.

Peripubertal psychological trauma was consistently associated with schizophrenia throughout the analyses. Although trauma is a heterogenous concept, a meta-analysis by Varese et al[36] showed that many studies exploring this subject have found a significantly increased risk of psychosis after exposure to trauma such as maltreatment and parental death. Sensitivity analyses revealed that *childhood* psychological trauma was also a significant risk factor for schizophrenia in both males and females as expected, but contrary to peripuberty, no significant interaction was found with prenatal infection. This emphasizes peripuberty as a period of particular susceptibility to traumatic experiences, especially when these occur in combination with other predisposing factors. Previous studies have shown higher risk estimates after exposure to childhood trauma compared to exposure at later developmental stages,[37,38] and it has been suggested that higher disease risk after childhood trauma might be a proxy for more prolonged exposure or higher risk of being exposed to trauma later in life.[18] This qualifies childhood psychological trauma as a true confounder, which should then be adjusted for as was done in the analyses.

Combined exposure to prenatal infection and peripubertal psychological trauma was associated with significantly higher risk compared to exposure to either alone. We found significant interaction on the multiplicative scale between peripubertal psychological trauma and infection, although only in males. These results thus corroborate the recent findings from animal studies where synergistic effects between prenatal infection and peripubertal stress were shown to lead to morphological, behavioral, and neurochemical changes relevant to schizophrenia.[21,22] Even though these studies did not report on any sex-specific effects,[21,22] it is interesting to note that the synergistic neuropathological effects between prenatal infection and peripubertal stress were more pronounced when the stressors were applied in early as compared to late peripubertal phases. It thus appears that the early peripubertal phase is particularly vulnerable to the adverse effects induced by traumatizing experiences, especially when the traumatic exposure takes place in combination with other predisposing factors such as prenatal infection.

The precise mechanisms underlying these associations remain elusive and may involve alterations in various developmental maturational processes. Conceptually, it has been proposed that prenatal infection may be a 'priming' factor that facilitates abnormal brain and behavioral development upon exposure to other environmental insults such as (early) peripubertal stress. Indeed, interference with early neurodevelopmental processes such as cell proliferation and migration may represent a common denominator for a range of environmental insults such as infection during pregnancy.[39] Such actions could be mediated via various pathological factors, including increased cytokine secretion, hormonal imbalances, and micro- and/or macro-nutritional deficiencies, all of which are critical for normal brain development.[12,40,41] Disturbances to early neurodevelopmental programs may increase the vulnerability of the offspring to changes in brain maturational processes in response to peripubertal trauma, and these changes may be sex specific as has been suggested.[17,26] Interference with maturational processes may involve abnormal synaptic pruning, which is one of the main events marking the transition of brain maturation from childhood to adolescence.[42] Synaptic pruning is of crucial importance to obtain a proper balance of inhibitory/excitatory neurons in the mature brain,[39,42] the disruption of which has been implicated in schizophrenia.[43]

Although we do see parallels to the recent findings obtained from animal studies,[21,22] the nature of register-based data and the way they are collected makes the translational aspect challenging, and correlation between exposures is probably far from the highly controlled environment of the natural experiment. Parental

socioeconomic status could be a proxy for social adversity, and has recently been shown to be robustly associated with schizophrenia risk in the offspring.[33] Parental death, somatic illness, history of crime, occupational situation, and family composition were all included as exposures and would inherently affect the socioeconomic status of the family. We have ruled out the alternative explanation that different rates of social adversities or levels of vitamin D in immigrants or individuals with a foreign background compared to native Danes were the cause of the associations observed,[44,45] because the cohort was restricted to children born in Denmark by parents born in Denmark. Also, this restriction ensured complete coverage of the cohort in regard to explanatory variables. In order to further adjust for confounding by socioeconomic status not directly related to the exposure, we included mother's and father's educational level the year prior to the offspring's birth, which only slightly attenuated the results.

Schizophrenia and infectious diseases have been associated with genetic markers in the human leukocyte antigens and the complement system,[46,47] and previous studies have indicated interaction between family history of psychosis and exposure to infection.[19,30,34] We therefore explored the pattern of results for individuals with and without a family history of psychiatric disorders to investigate whether they could be explained by genetic vulnerability in these individuals, and found no support for this alternative hypothesis. However, psychiatric family history is probably too crude a marker of variation in individual genes to exclude genetic stratification. In contrast to the previous studies that found interaction between psychiatric family history and infection on the additive scale,[19,30,34] we only investigated interaction on the multiplicative scale and the results are difficult to compare.

Determining synergistic effects of infection and other environmental adversities during critical periods may offer valuable insight into etiological mechanisms relevant to schizophrenia and other neuropsychiatric disorders with neurodevelopmental components. In the present study, we did not have enough power to stratify by trimester of exposure or subdivide the postnatal periods of exposure into eg, early and late peripubertal phases. If future research replicates synergistic effects of prenatal exposure to infection and psychological trauma, particular emphasis should be placed on the aspect of timing and on the relative contribution of specific traumatizing factors.

Methodological Considerations

With a minimum age of 15 and a maximum age of 33, this constitutes a relatively young cohort for studying schizophrenia, and the proportion of individuals with a schizophrenia spectrum diagnosis in the cohort (0.99%) is probably underestimated compared to the Danish population.[48] Using Cox regression in the analyses takes this into account, by estimating the risks based on number of individuals of the same age per population at risk per day. Although the peak of incidence for schizophrenia spectrum disorder is around the same age for males and females in the Danish population in the ICD-10 period,[48] the female population may still include proportionally more people who will go on to develop schizophrenia after the end of the observation period. A longer period of follow-up could diminish the stark sex differences observed, and a word of caution is warranted in the interpretation.

Maternal infections during pregnancy were measured through data covering medical hospital admissions. As most infections supposedly do not lead to hospital contact, we most likely have captured only the most severe cases, exhibiting symptoms serious enough to be admitted. We must therefore expect some degree of non-differential misclassification of the exposure biasing our results towards no association between infection during pregnancy and later development of schizophrenia.

Although the associations found in the study are robust, observational epidemiology is incapable of distinguishing true causation from association originating from confounding or reverse causation. Therefore, caution is warranted when interpreting the results.

Conclusion

In conclusion, our study provides the first epidemiological evidence for the hypothesis that exposure to prenatal infection and psychological trauma in peripubertal life can act in synergy to increase the risk of schizophrenia in male subjects. Future studies are warranted to further examine the role of postnatal timing and sex-specific effects in this association.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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