Psychological Medicine (2013), **43**, 239–257. © Cambridge University Press 2012
doi:10.1017/S0033291712000736

REVIEW ARTICLE

Prenatal maternal infection, neurodevelopment and adult schizophrenia: a systematic review of population-based studies

G. M. Khandaker[1,2]*, J. Zimbron[1,2], G. Lewis[3] and P. B. Jones[1,2]

[1] *Department of Psychiatry, University of Cambridge, UK*
[2] *Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, UK*
[3] *Academic Unit of Psychiatry, University of Bristol, UK*

Background. Disruption of foetal development by prenatal maternal infection is consistent with a neurodevelopmental model of schizophrenia. Whether specific prenatal infections are involved, their timing and the mechanisms of any effect are all unknown. We addressed these questions through a systematic review of population-based studies.

Method. Electronic and manual searches and rigorous quality assessment yielded 21 studies that included an objective assessment of individual-level prenatal maternal infection and standardized psychotic diagnoses in adult offspring. Methodological differences between studies necessitated a descriptive review.

Results. Results for prenatal maternal non-specific bacterial, respiratory or genital and reproductive infection differed between studies, which reported up to a two- to fivefold increased risk of schizophrenia. Evidence for herpes simplex virus type 2 (HSV-2) and *Toxoplasma gondii* was mixed; some studies reported up to a doubling of schizophrenia risk. Prenatal HSV-1 or cytomegalovirus (CMV) infections were not associated with increased risk. Exposure to influenza or other infections during early pregnancy may be more harmful than later exposure. Increased proinflammatory cytokines during pregnancy were also associated with risk. Prenatal infection was associated with structural and functional brain abnormalities relevant to schizophrenia.

Conclusions. Prenatal exposure to a range of infections and inflammatory responses may be associated with risk of adult schizophrenia. Larger samples, mediation and animal models should be used to investigate whether there is a 'sensitive period' during development, and the effects of prenatal infections on neurodevelopment. Inclusion of genetic and immunological information should help to elucidate to what extent genetic vulnerability to schizophrenia may be explained by vulnerability to infection.

Received 7 December 2011; Revised 9 March 2012; Accepted 12 March 2012; First published online 16 April 2012

Key words: Cytokines, infection, neurodevelopment, pregnancy, schizophrenia.

Introduction

Maternal infection during pregnancy with *Toxoplasma gondii*, rubella, cytomegalovirus (CMV), herpes simplex virus (HSV) and other microbes (i.e. TORCH infections) have long been known to be associated with mental retardation, cerebral hypoplasia, ventriculomegaly and other brain and behavioural abnormalities in the offspring (Remington *et al*. 2006). The neurodevelopmental theory of schizophrenia postulates abnormalities in early neurodevelopment as a possible cause of the disorder (Murray & Lewis, 1987; Weinberger, 1987). Empirical evidence for this theory comes from birth cohort studies demonstrating delays in motor milestone, and deficits in pre-morbid cognitive function in future cases of schizophrenia (Jones *et al*. 1994; Khandaker *et al*. 2011). Consequently, several studies have investigated links between maternal infection during pregnancy and risk of schizophrenia in adult offspring.

Many of the early investigations on this topic were based on data from influenza epidemics (Mednick *et al*. 1988), which yielded conflicting results (Selten *et al*. 2010). These studies defined maternal exposure to influenza as being pregnant at the time of an epidemic rather than direct measurement of exposure at the individual level. Thus, the ecological fallacy could be a reason for their discrepant findings (Selten *et al*. 2010). More recent studies based on general population

* Address for correspondence: Dr G. M. Khandaker, Department of Psychiatry, University of Cambridge, Box 189, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK.
(Email: gmk24@medschl.cam.ac.uk)

cohorts have overcome this issue. These have used objective measures to determine exposure to infection during the prenatal period at the individual level (Susser, 1999; Susser *et al*. 2000; Buka *et al*. 2001*a*; Mortensen *et al*. 2007; Susser *et al*. 2011). Findings from these studies merit further attention, as they may provide a better understanding of the true nature of this association.

A previous review implicated several prenatal maternal infections with increased risk of schizophrenia in adult offspring (Brown & Derkits, 2010). However, fundamental questions have yet to be settled. These include the timing of prenatal infection or any links between prenatal infection and structural and functional brain abnormalities associated with schizophrenia. These issues are important because they would provide important clues to the relevance of prenatal infections in the causation of adult psychotic disorders. Therefore, associations between prenatal infection and neurodevelopmental outcomes in offspring are of much interest in current epidemiological and preclinical research (Meyer & Feldon, 2010; Brown *et al*. 2011). We have carried out a systematic review of robust population-based studies to address the following issues: (i) association between adult psychotic illness and specific types of prenatal maternal infection, (ii) association between risk and timing of prenatal infection, and (iii) effects of prenatal infection on neurodevelopment. We have included three new studies published on this topic since the most recent review, contributing evidence on a further 4000 cases and more than 1.1 million controls (Xiao *et al*. 2009; Mortensen *et al*. 2010; Nielsen *et al*. 2011). Findings from these studies provide a new insight into the nature of the association between prenatal maternal infection and psychosis in offspring. We also discuss the biological plausibility of such associations in view of recent human and preclinical research.

Method

Search strategy

We searched Medline, PubMed and EMBASE databases from their respective inceptions to November 2011 for studies of prenatal infection that were based on human samples and published in the English language. Search terms included indexing terms (e.g. MeSH) and free texts: [(prenatal OR in utero OR foetal OR maternal) AND (infection OR inflammation OR illness) AND (schizophrenia OR psychotic disorder)]. We also identified potential studies in the reference lists of included studies and wrote to prominent authors in this field for any further relevant studies.

Study selection

Included studies (i) were based on general population datasets, (ii) cohort or nested case–control in design, (iii) used serological assays or clinical examination to determine exposure to infection during the prenatal period at the individual level and (iv) used contemporary ICD or DSM directions to define the outcome of schizophrenia, non-affective psychosis, affective psychosis and other psychotic disorders. Studies that used self-report of exposure to infections instead of clinical examination or serology were excluded. Genetic high-risk studies and studies that used aggregate data to define exposure, for example pregnancy at the time of an epidemic or incidence or prevalence of certain infection during pregnancy rather than direct measurement of infection at the individual level, were also excluded.

Data extraction

Electronic search and study selection were carried out by two researchers working independently (G.M.K. and J.Z.). They examined all titles and abstracts, obtained full texts of potentially relevant papers and applied inclusion criteria. Any differences in opinion were resolved through discussions with the wider study team. All studies that met inclusion criteria were critically appraised using the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) checklists for observational studies (von Elm *et al*. 2007), with focus on sampling, measurement of exposure and outcome, follow-up, attrition, analytical strategy, bias, confounding and other methodological issues. At this stage, studies with serious methodological concerns that might have biased their findings were identified and excluded from the review.

Data synthesis and rationale for not proceeding to meta-analysis

There was considerable variation among selected studies with regard to design, measurement of prenatal infection, definition of outcome and methods of case ascertainment. For example, three studies investigated links between schizophrenia and maternal exposure to HSV type 2 (HSV-2) during the prenatal period. To define exposure, one study used the ratio of anti-HSV-2 immunoglobulin (Ig)G concentration between cases and controls (Buka *et al*. 2008). The rest of the studies used absolute concentration of IgG in maternal serum (Brown *et al*. 2006; Mortensen *et al*. 2010). Again, the cut-off values used to define exposure were not the same between these two studies (issues around exposure measurement are considered in detail in the

https://doi.org/10.1017/S0033291712000736 Published online by Cambridge University Press

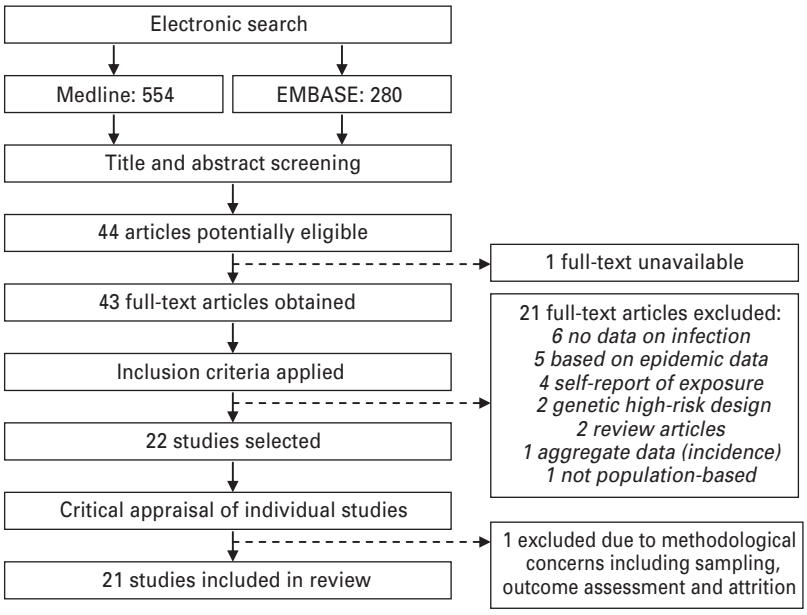

Fig. 1. Study selection process for the systematic review.

discussion section). Definitions of outcomes were also different. For example, two studies used non-affective psychosis by DSM-IV (Brown *et al*. 2006; Buka *et al*. 2008) whereas one used schizophrenia by ICD-10 (Mortensen *et al*. 2010). Such differences in exposure and outcome measurements were also observed for other infections. Because of this heterogeneity the results of meta-analyses would be difficult to interpret and we therefore present a descriptive review of the studies.

Results

Twenty-one studies were included in the review (Fig. 1). There were 16 studies concerning risk of adult psychotic illness. One of these studies also examined childhood IQ in relation to exposure to influenza in the prenatal period. Five studies looked exclusively into structural and functional brain abnormalities related to schizophrenia. Excluded studies with reasons for exclusion are presented as online supplementary material in Table S1.

Prenatal maternal infection and schizophrenia and other psychoses in adult offspring

We reviewed 16 studies on this topic (Brown *et al*. 2000, 2004*a*, *b*, 2005, 2006; Buka *et al*. 2001*a*, *b*, 2008; Babulas *et al*. 2006; Mortensen *et al*. 2007; Clarke *et al*. 2009; Ellman *et al*. 2009; Sorensen *et al*. 2009; Xiao *et al*. 2009; Mortensen *et al*. 2010; Nielsen *et al*. 2011). Eleven of these studies were based on two US birth cohorts, the National Collaborative Perinatal Project (NCPP) cohort (Susser, 1999; Susser *et al*. 2011) and the Prenatal Determinants of Schizophrenia (PDS) cohort (Susser *et al*. 2000). The PDS cohort (Susser *et al*. 2000) was derived from the Child Health and Development Study (CHDS; van dan Berg *et al*. 1988), a prospective birth cohort study of factors affecting outcomes of pregnancy and child development. The NCPP is a multicentre prospective cohort study involving 13 sites. Studies included in the present review are all based on the samples from Providence, Boston and Philadelphia; together, the first two sites are known as the New England Family Study (Susser, 1999; Susser *et al*. 2011). The remaining five studies were based on general population cohorts from Denmark and Finland. Characteristics of these cohorts and assessment of exposure and outcome in studies based on these cohorts are presented in Table 1.

To define exposure, five studies used prospectively collected records of clinically diagnosed infection. Nine studies used serological assays for various antimicrobial antibodies in maternal blood samples obtained during pregnancy, and a further two used inflammatory cytokines as a proxy of exposure to infections. Serological studies were all nested case–control in design whereas the studies of clinically diagnosed infection involved analyses of entire cohorts. We have summarized the results of 'serological' and 'clinically diagnosed' studies separately, including effect of adjustment for confounding factors in Table 2 (for an extended version of this table see Table S2 in the online supplementary material). Strengths and weaknesses of individual studies are presented in Table 3.

https://doi.org/10.1017/S0033291712000736 Published online by Cambridge University Press

Table 1. *Cohort characteristics and assessment of exposure and outcome in studies of prenatal infection*

Name of cohort	Cohort characteristics	Duration of follow-up	Source, type and timing of exposure sample	Outcomes and diagnostic criteria	Case ascertainment
NCPP, USA	Born between 1959 and 1966; $n=25\,025$ in Providence, Boston and Philadelphia sites combined	Up to age 35 years	Maternal serum collected during late pregnancy or at delivery used for serological tests for specific infections and cytokines	Affective and non-affective psychosis[a] by DSM-IV	Boston and Providence: interview and/or record linkage with psychiatric treatment facilities to identify potential cases, followed by interview using SCID or medical chart review to establish diagnosis Philadelphia: screening of psychiatric database followed by chart review
PDS, USA	Born between 1959 and 1966; $n=12\,094$	Up to mid-thirties	Serology in maternal serum collected during pregnancy and delivery, and clinically diagnosed infection during pregnancy	SSD[b] by DSM-IV	Psychiatric in- and out-patient registers and pharmacy registers were screened for potential cases, followed by diagnosis through interview using DIGS or case-note review
Danish register-based cohorts	Individuals born since 1981	Up to age 18 and 25 years	Blood spots on filter paper obtained from 5–7-day-old neonates used for immunoassay	Schizophrenia by ICD-10	Danish National Psychiatric Register
Copenhagen perinatal cohort	Born between 1959 and 1961; $n=9125$	Up to 47 years	Clinically diagnosed and/or treated maternal infection (bacterial or viral) during pregnancy	Schizophrenia by ICD-8 and ICD-10	Danish National Psychiatric Register
Finnish cohort	Individuals born in Helsinki between 1947 and 1990	–	Maternal hospitalization for pyelonephritis during pregnancy	Schizophrenia by ICD-8 to ICD-10	Finnish Hospital Discharge Register

NCPP, National Collaborative Perinatal Project; PDS, Prenatal Determinants of Schizophrenia; DIGS, Diagnostic Interview for Genetic Studies; SSD, schizophrenia spectrum disorder.

[a] Includes schizophrenia, schizo-affective, other non-affective psychosis, schizo-affective bipolar type, bipolar disorder with psychotic features, major depressive disorder with psychotic features and psychosis not otherwise specified (NOS).

[b] Includes schizophrenia, delusional disorder, psychotic disorder NOS, schizo-affective disorder and schizotypal personality disorder.

Table 2. *Population-based studies of prenatal infection and schizophrenia and other psychosis*

Study	Setting and design	Case/control	Case definition	Exposures measured	Adjustment for confounding	Main findings
Serological studies of specific infection						
Buka *et al*. 2001*a*	NCPP, nested case–control	27/54	Affective and non-affective psychosis by DSM-IV	CMV, rubella, *Toxoplasma gondii*, human parvovirus B19, HSV-1, HSV-2 and *Chlamydia*	Gender, ethnicity, age, social class, maternal mental illness, weight gain and smoking in pregnancy	Elevated IgG to HSV-2 in case mothers, no increase in IgG to HSV-1, CMV, *T. gondii* or rubella
Buka *et al*. 2008	NCPP, nested case–control	200/544	Affective and non-affective psychosis by DSM-IV	HSV-2	Birth city and season, gender, ethnicity, maternal education and parental mental illness	Adjusted OR (95% CI) for schizophrenic psychosis for maternal HSV-2 seropositivity 1.8 (1.1–3.0)
Xiao *et al*. 2009	NCPP, nested case–control	219/618	Affective and non-affective psychosis by DSM-IV	*T. gondii* (serotype I, II and III)	Birth city, age, gender and ethnicity	Adjusted OR for affective psychosis 5.24 (95% CI 1.69–16.49) for exposure to *T. gondii* type I
Ellman *et al*. 2009	NCPP, nested case–control	96/274	Affective and non-affective psychosis by DSM-IV	Influenza	Maternal ethnicity, social class and offspring gender	Non-significant 1.7-fold increased risk of schizophrenia for influenza B
Brown *et al*. 2004*a*	PDS, nested case–control	64/125	SSD by DSM-IV	Influenza	Maternal age, gender and gestational age of foetus	Unadjusted OR (95% CI) for SSD for influenza in first trimester 7.0 (0.7–75.3) and in first half of pregnancy 3.0 (0.98–10.1)
Brown *et al*. 2005	PDS, nested case–control	63/123	SSD by DSM-IV	*T. gondii*	Date of birth, gender and maternal age	Adjusted OR for SSD 2.61 (95% CI 1.00–6.82) for maternal 'high' *versus* 'low' IgG antibody titre
Brown *et al*. 2006	PDS, nested case–control	60/110	SSD by DSM-IV	HSV-1, HSV-2 and CMV	Age, gender, maternal ethnicity and education	No association between SSD and HSV-1, HSV-2 or CMV
Mortensen *et al*. 2007	Danish, nested case–control	71/648	Schizophrenia by ICD-10	*T. gondii* and HSV	Year and place of birth, gender, family history of mental illness	OR for schizophrenia 1.79 (95% CI 1.01–3.15) for *T. gondii* seropositivity (IgG); HSV-1 and -2: no association with schizophrenia/ schizo-affective disorder
Mortensen *et al*. 2010	Danish, nested case–control	602/602	Schizophrenia by ICD-10	HSV-2	Gender, family history of mental illness, urbanization at place of birth, immigrant status and parental age	Incidence rate ratio for schizophrenia 1.51 (95% CI 1.08–2.10) using cut-off value of $\geqslant$0.2 for serum IgG

Table 2 (*cont.*)

Study	Setting and design	Case/control	Case definition	Exposures measured	Adjustment for confounding	Main findings
Serological studies of inflammatory cytokines						
Buka *et al*. 2001*b*	NCPP, nested case–control	27/54	Affective and non-affective psychosis by DSM-IV	IL-1β, IL-2, IL-4, IL-8, TNF-α	Gender, ethnicity, age, social class, maternal mental illness, weight gain and smoking in pregnancy	Increased TNF-α in case mothers; OR for psychosis 8.5 ($p<0.03$) in offspring of women with both third trimester infection and TNF-α levels >75th percentile of control sample
Brown *et al*. 2004*b*	PDS, nested case–control	59/118	SSD by DSM-IV	IL-1β, IL-6, IL-8, TNF-α	Foetal age, gender, maternal age, social class, ethnicity	Nearly twofold increase in mean and median values of IL-8 at second/third trimester in case mothers
Studies of clinically diagnosed infection						
Brown *et al*. 2000	PDS, prospective cohort	58/7781	SSD by DSM-IV	Respiratory infection[a]	Maternal ethnicity, education and smoking during pregnancy	Second-trimester infection: adjusted OR for SSD 2.13 (95% CI 1.05–4.35), schizophrenia 2.07 (95% CI 0.8–5.36)
Babulas *et al*. 2006	PDS, prospective cohort	71/7723	SSD by DSM-IV	Genital/reproductive infection[b]	Maternal age, ethnicity, education and mental illness	Periconceptional infection: adjusted rate ratio for SSD 5.03 (95% CI 2.00–12.64); no increased risk for infection during pregnancy
Clarke *et al*. 2009	Finnish retrospective national cohort	9596 exposed *v*. 13 808 unexposed	Schizophrenia by ICD-8 to ICD-10	Pyelonephritis	–	First-trimester infection, OR 3.35 (95% CI 0.8–14.0); risk difference 0.51% in those with a positive family history *versus* 0.10% in those without such history
Sorensen *et al*. 2009	Copenhagen, prospective cohort	153/7788	Schizophrenia by ICD-8 and ICD-10	Bacterial and viral infection[c]	Social class and use of analgesics in pregnancy	First-trimester bacterial infection: schizophrenia risk by age 34, adjusted OR 2.53 (95% CI 1.07–5.96), by age 47, adjusted OR 2.14 (95% CI 1.06–4.31)

Nielsen *et al*. 2011	Danish register-based cohort	3722/1 115 752	Schizophrenia by ICD-8 to ICD-10	Maternal and paternal hospitalization for infection[d]	Parental history of schizophrenia, age and gender	Adjusted risk ratio for maternal second-trimester infection 1.72 (95% CI 1.15–2.46), infection any time in the past before, during or after pregnancy 1.24 (95% CI 1.16–1.33); paternal infection any time in the past 1.14 (95% CI 1.05–1.23)

NCPP, National Collaborative Perinatal Project; PDS, Prenatal Determinants of Schizophrenia; SSD, schizophrenia spectrum disorder; CMV, cytomegalovirus; Ig, immunoglobulin; HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2; IL, interleukin; TNF, tumour necrosis factor; OR, odds ratio; CI, confidence interval.

[a] Maternal respiratory infections included tuberculosis, influenza, influenza with pneumonia, bronchopneumonia, atypical pneumonia, pleu-risy, emphysema/viral respiratory infections, acute bronchitis, and upper respiratory infections.

[b] Genital/reproductive infections included endometritis, cervicitis, pelvic inflammatory disease, vaginitis, syphilis, condylomata, 'venereal disease' and gonorrhoea. Periconceptional period = 30 days before and after last menstrual period.

[c] Bacterial infections included sinusitis, tonsillitis, pneumonia, cystitis, pyelonephritis, bacterial venereal infection, and any other bacterial infection. A viral infection was judged to be present if (1) a medical diagnosis had been made (commonly by the general practitioner) or (2) symptoms consistent with minor respiratory illnesses or influenza had been present and the mother had been confined to bed and had a rise in temperature to at least 38 °C.

[d] Infections include general infections, skin infections, respiratory infections, infections related to puerperium (mothers), genital and other infections.

Serologically determined prenatal maternal infection

HSV

Three out of five studies reported a statistically significant increased risk of schizophrenic psychosis in the adult offspring for exposure to HSV-2 infection during pregnancy (Buka *et al*. 2001*a*, 2008; Mortensen *et al*. 2010). These studies used elevated levels of IgG antibodies to HSV-2 to define exposure, that is seropositivity. A recent Danish study involving 602 cases reported a statistically significant 50% increased risk of adult schizophrenia for prenatal exposure to HSV-2 (Table 2). Risk was slightly attenuated (but still statistically significant) only after adjustment for family history of mental illness (Mortensen *et al*. 2010). This risk estimate is in line with a previous report from the NCPP birth cohort (Buka *et al*. 2008).

One study from the PDS cohort reported a 30% increase in risk of schizophrenia spectrum disorder (SSD) for maternal HSV-2 seropositivity during late pregnancy (Brown *et al*. 2006), but this was not statistically significant. The study also reported similar results for exposures to HSV-1 and CMV. A Danish study also reported no increase in risk of schizophrenia for prenatal exposure to HSV-1 and -2 (Mortensen *et al*. 2007).

T. gondii

Elevated levels of maternal IgG antibodies to *T. gondii* were reported to be associated with increased risk of schizophrenic psychosis from two cohorts (Brown *et al*. 2005; Mortensen *et al*. 2007). One study from the PDS cohort (Brown *et al*. 2005) found a more than twofold increase in risk of SSD for maternal 'high' IgG antibody titre ($\geqslant$1:128) during late pregnancy, compared to 'low' titre ($<$1:16), with an odds ratio (OR) of 2.61 and 95% confidence interval (CI) 1.00–6.82. Similar findings (OR 1.79) were observed in the Danish study (Mortensen *et al*. 2007), which also suggested that elevated maternal IgG to *T. gondii* was associated specifically with risk of schizophrenia, out of all four outcomes included in the analysis.

One study involving the largest number of cases (n = 219) and controls to date investigated prenatal exposure to three specific serotypes of *T. gondii* in relation to affective and non-psychosis in adult offspring (Xiao *et al*. 2009). Infection with *T. gondii* Type I (out of all three serotypes) was reported to be associated with increased risk of affective psychosis (more than fivefold) but not non-affective psychosis (Table 2). However, analysis of non-affective psychosis was based on an insufficient sample size of 11 cases and 29 controls.

Table 3. *Strengths and weaknesses of individual studies*

Study	Strengths	Weaknesses
NCPP birth cohort		
Buka *et al*. 2001*a*	Studied several exposures, included several immunoglobulins, two-stage attempt to case identification	Small sample and heterogeneous case group; for some cases used maternal IgG levels without having documented seropositivity
Buka *et al*. 2001*b*	First to investigate inflammatory cytokines in these studies, included several cytokines	Small sample and heterogeneous case group
Buka *et al*. 2008	Large sample allowing study of schizophrenic and affective psychosis separately	Broad definition of case; in some cases diagnosis were made by chart review; overall high seropositivity in sample due to high seropositivity among African-Americans
Xiao *et al*. 2009	Large sample, studied three serotypes of *Toxoplasma gondii*	Broad definition of case; in some cases diagnoses were made by chart review
Ellman *et al*. 2009	Examined childhood IQ and also adult schizophrenia with regard to foetal exposure to influenza	Small sample, broad definition of cases
PDS birth cohort		
Brown *et al*. 2000	Analysed entire cohort, large sample	Broad exposure of respiratory infections, under-reporting of exposure and misclassification of timing of exposure is possible
Brown *et al*. 2004*a*	First serological study of prenatal influenza, good estimate of timing of exposure	Exposure based on proxy measure of seroconversion but validated in a comparison sample with seroconversion data
Brown *et al*. 2004*b*	Larger sample size compared to a similar previous study, included several cytokines	Median values of one cytokine (TNF-α) was lower than in most studies of this cytokine
Brown *et al*. 2005	Two-stage exposure assessment, use of more sensitive tests than previous studies	Small sample size
Brown *et al*. 2006	Outcome more focused than previous studies, analysis restricted to seropositive mothers	Small sample size
Babulas *et al*. 2006	Analysed entire cohort, large sample	Broad exposure definition, small number of exposed cases ($n=5$)
Danish cohorts		
Mortensen *et al*. 2007	Large sample size	Blood samples were missing for 28% of eligible cases, short follow-up
Sorensen *et al*. 2009	Analysed entire cohort, large sample, examined both narrow and broad schizophrenia	Broad categories of exposure, viral and bacterial infections, misclassification possible
Mortensen *et al*. 2010	Large sample size, detail family psychiatric history taken into account	Short follow-up
Nielsen *et al*. 2011	Large sample, included paternal infection and maternal infection before and after pregnancy, family history of schizophrenia taken into account	Only able to use hospital admission for infection as exposure; limited power for analysis of infection during pregnancy
Finnish cohort		
Clarke *et al*. 2009	Large sample size, used sibling comparison group, precise timing of exposure using hospital admission data	Small number of cases meant low statistical power to examine each trimester of pregnancy

NCPP, National Collaborative Perinatal Project; PDS, Prenatal Determinants of Schizophrenia; IgG, immunoglobulin G; TNF-α, tumour necrosis factor-α.

Influenza

Two studies were available. One was based on the PDS birth cohort and reported a sevenfold increased risk of SSD for exposure during the first trimester and a threefold increased risk for exposure during the first half of pregnancy (Brown *et al*. 2004*a*). However, the sample size was relatively small and none of the risk estimates were statistically significant (Table 2). There was no increase in risk for exposure during late pregnancy. The second study was from the NCPP birth cohort and it assayed maternal blood samples collected at delivery for IgG antibodies to influenza B virus and reported a non-significant 70% increase in risk of schizophrenia in the adult offspring (Ellman *et al*. 2009).

Inflammatory cytokines

One study from the NCPP cohort suggested that inflammatory cytokines may mediate risk of psychosis related to prenatal infection (Buka *et al*. 2001*b*). Among 27 cases of affective and non-affective psychosis and 54 matched controls, Buka *et al*. (2001*b*) found that mean tumour necrosis factor (TNF)-α level was significantly higher in case mothers. Furthermore, adult offspring of women with both clinical report of third trimester infection and elevated TNF-α level were eight times more likely to develop psychosis. However, this analysis was based on a small sample. A similar study based on the PDS cohort reported a nearly twofold increase in mean and median values of interleukin (IL)-8 during mid- to late pregnancy in SSD case mothers (Brown *et al*. 2004*b*). This association was unchanged in analysis restricted to cases of schizophrenia only.

Clinically diagnosed prenatal maternal infection

General infections

In a large Danish cohort maternal hospitalization for infection during pregnancy was associated with increased risk of schizophrenia in offspring [risk ratio (RR) 1.39, 95% CI 1.18–1.62; Nielsen *et al*. 2011]. Only second-trimester infection was statistically significant (RR 1.72, 95% CI 1.15–2.46). Of note, maternal infection any time in the past (before, during or after pregnancy combined) was also associated with increased risk of schizophrenia (RR 1.24, 95% CI 1.16–1.33). Maternal infection during pregnancy was not significantly different from that before or after pregnancy in terms of offspring's risk of schizophrenia (Nielsen *et al*. 2011).

In the Copenhagen Perinatal Cohort bacterial infection during the first trimester was reported to be associated with a nearly twofold increased risk of schizophrenia at follow-up at both age 34 and 47 years (Sorensen *et al*. 2009) (Table 1). Risk was also increased, but not statistically significant, for second-trimester exposure to bacterial infections. There was no significant increase in risk for viral infections. However, broad definitions of bacterial and viral infection were used in this cohort.

Respiratory infection

In an analysis of the entire PDS cohort, maternal respiratory infection during the second trimester was reported to be associated with a twofold increased risk of SSD in adult offspring (Brown *et al*. 2000). A similar increase in risk was observed for schizophrenia. Most exposed cases suffered from an upper respiratory tract infection. Similarly, in the Copenhagen Perinatal Cohort maternal upper respiratory infection during any time in pregnancy was associated with a threefold increased risk of schizophrenia in the offspring by age 47 years.

Genital, reproductive and urinary infection

Maternal genital or reproductive infection during the periconceptional period (i.e. 30 days before and after the last menstrual period) was associated with a fivefold increased risk of SSD in adult offspring in the PDS cohort (Babulas *et al*. 2006). However, there was no increase in risk for such infections during pregnancy (first, second or third trimester). In another study, maternal hospital admission for genital infection during pregnancy was associated with a twofold increased risk of schizophrenia in adult offspring (Nielsen *et al*. 2011). Similarly, in the Copenhagen Perinatal Cohort maternal gonococcal infection during any time in pregnancy was associated with a more than threefold increased risk of schizophrenia by age 47 years (Sorensen *et al*. 2009). One Finnish study did not find any significant association between maternal hospitalization with pyelonephritis during pregnancy and risk of schizophrenia in the offspring (Clarke *et al*. 2009).

Timing of prenatal maternal infection and risk of adult schizophrenia

Most studies lacked power to address the issue of a 'sensitive period', that is maternal infection during which stage of pregnancy may be most harmful. However, in general we observed a trend for greater risk of adult psychotic illness for exposure to infections during early stages of gestation (Table 4). This needs to be interpreted in the context of significant

https://doi.org/10.1017/S0033291712000736 Published online by Cambridge University Press

Table 4. *Timing of prenatal infection and risk of schizophrenia and other psychotic disorders in adult offspring*

Time of exposure	Infectious agent	Effect size[a]	Study	Cohort
Around conception	Genital/reproductive infection	5	Babulas *et al*. 2006	PDS
First trimester	Influenza	7	Brown *et al*. 2004*a*	PDS
	Bacterial infection	2	Sorensen *et al*. 2009	Copenhagen perinatal cohort
Second trimester	Influenza[b]	3	Brown *et al*. 2004*a*	PDS
	Respiratory infection	2	Brown *et al*. 2000	
Third trimester or at delivery	HSV-2	1.5	Buka *et al*. 2001, 2008 and Xiao *et al*. 2009	NCPP
	Toxoplasma gondii	2	Brown *et al*. 2005	PDS
			Mortensen *et al*. 2007, 2010	Danish cohorts

NCPP, National Collaborative Perinatal Project; PDS, Prenatal Determinants of Schizophrenia; HSV-2, herpes simplex virus type 2.

[a] Only studies that reported an increase in risk in relation to prenatal infection were included in this table; approximate point estimates shown for guide purpose only; heterogeneity in exposure measurement, case definition, analysis and measure of risk exists between individual studies, refer to Table 1 for individual study details and results.

[b] Early second-trimester exposure.

variation among studies in design, exposure and outcome measurement.

Interaction between prenatal maternal infection and other risk factors

Family history of psychosis

Using an additive model, a Finnish study reported evidence of an interaction between family history of psychosis and maternal pyelonephritis during pregnancy (Clarke *et al*. 2009). In a stratified analysis, the risk difference between those exposed and those unexposed to prenatal infection in the group with a family history of psychosis was five times larger than the risk difference in those without such history.

Preterm birth

In the largest study of HSV-2, involving 602 cases, there was an indication that the incidence rate ratio (IRR) for schizophrenia is slightly higher among exposed individuals born before 36 weeks of gestation (IRR 3.68, 95% CI 0.76–17.79) compared to those born at term (IRR 1.52, 95% CI 1.13–2.03). However, this estimate was based on small numbers: only seven exposed cases and two exposed controls were born preterm (Mortensen *et al*. 2010).

Maternal sexual and reproductive behaviour

One study from the NCPP birth cohort reported that the mother's sexual behaviour prior to and during pregnancy was relevant to HSV-2 seropositivity and subsequent risk of psychotic illness in the offspring (Buka *et al*. 2008). Rates of HSV-2 seropositivity at delivery were similar among case and control mothers who reported use of contraception or lower frequency of intercourse during pregnancy. By contrast, case mothers who reported frequent intercourse or no use of contraception were twice as likely to be seropositive than control mothers.

Prenatal maternal infection and structural and functional brain abnormalities in schizophrenia

We identified six population-based studies, mostly from the PDS and NCPP birth cohorts (Table 5) (Brown *et al*. 2001, 2009*a*, *b*, 2011; Ellman *et al*. 2009, 2010). Maternal infection or increased inflammatory cytokines during pregnancy were reported to be associated with both structural and functional brain phenotypes relevant to schizophrenia in the offspring.

Exposed cases were reported to show significant deficit in childhood and adult verbal IQ, and greater IQ decline during the pre-morbid period. Exposed cases were also reported to show increased ventricular volume, increased length of the cavum septum pallucidum, reduced cortical volume and deficits in executive function in adulthood. However, prenatal infections did not seem to affect some of these parameters, such as childhood verbal IQ or adult ventricular and cortical volume in exposed healthy controls (Ellman *et al*. 2009, 2010). Some of these studies did not include a healthy comparison group (Brown *et al*. 2009*a*, 2011).

Discussion

A possible role of infection and immunity in the aetiology of psychotic illness has been in the focus of

https://doi.org/10.1017/S0033291712000736 Published online by Cambridge University Press

Table 5. *Prenatal infection and structural and functional brain abnormalities relevant to schizophrenia*

Study	Study design	Prenatal exposure	Main findings
Brown *et al*. 2009	PDS cohort: structural brain anomaly in 20 cases of DSM-IV SSD and seven controls, 12 cases exposed to prenatal infections	Influenza, respiratory infection, toxoplasma or maternal/genital reproductive infection measured by immunoassay or clinical diagnosis	CSP length, mean (S.D.) in mm by group: exposed case ($n=12$) 4.67 (3.65), unexposed case ($n=8$) 1.75 (2.87), exposed controls 4.2 (1.4), unexposed controls 0.35 (0.7). For exposed cases, 11 of 12 (92%) had CSP length >1.4 mm. For unexposed cases, six of eight (75%) had CSP length of $\leqslant 1.4$ mm
Ellman *et al*. 2010	PDS cohort: structural brain anomaly in 17 cases of DSM-IV SSD and eight controls	Concentration of inflammatory cytokine IL-8 in maternal blood samples collected at second/third trimester	Among cases, increased IL-8 was associated with significant increase in ventricular cerebrospinal fluid, significant decrease in cortical volume in left entorhinal cortex and right posterior cingulate. No significant association in controls
Brown *et al*. 2009	PDS cohort: executive function in 24 cases of DSM-IV SSD, eight cases exposed to prenatal infections	Influenza during first half of pregnancy or *Toxoplasma gondii* at third trimester or at delivery	Exposed cases had increased number of total error, preservative error and non-preservative error in the Wisconsin Card Sorting Test, and increased mean time in Part B of the Trail Making Test
Brown *et al*. 2011	Subset of PDS cohort: adult motor and cognitive function in 25 cases of SSD (11 exposed and 14 unexposed)	Genital and reproductive infection during any time in pregnancy	Exposed cases performed significantly worse on verbal memory and fine motor coordination. In stratified analysis, these differences were significant only in the African-American group
Ellman *et al*. 2009	NCPP cohort: IQ at age 7 years by WISC in 96 cases (60 schizophrenia and 36 affective psychoses) and 274 controls	Maternal influenza in samples collected at delivery, exposure = IgG antibody titre >75th percentile	Exposed cases performed worse on verbal IQ (SMD 0.408, $p=0.024$) and in the information subset (SMD 0.37, $p=0.04$) than unexposed cases. No significant difference in any measure of IQ between exposed and unexposed controls
Brown *et al*. 2001	Rubella Birth Defects Evaluation Project, New York: follow-up of 53 cases until age 33 years for DSM-IV SSD, cognitive function measured in childhood and in adolescence	Congenital rubella	20.8% developed SSD (5.7% schizophrenia), 26.4% affective disorder, 41.5% no psychiatric illness; cognitive decline between childhood and adolescence in 87.5% cases of SSD *v.* 37.0% in non-SSD group; degree of IQ decline greater in SSD group than non-SSD group (average IQ decline 11 points *v.* 3 points respectively)

PDS, Prenatal Determinants of Schizophrenia; SSD, schizophrenia and spectrum disorder; NCPP, National Collaborative Perinatal Project; WISC, Wechsler Intelligence Scale for Children; IL-8, interleukin 8; IgG, immunoglobulin G; CSP, cavum septum pallucidum; S.D., standard deviation; SMD, standardized mean difference.

neuropsychiatric research for more than a century (Menninger, 1994). Potential disruption of foetal development from prenatal maternal infections is in keeping with the neurodevelopmental theory of schizophrenia. Our review of robust epidemiological evidence suggests that exposure to infectious agents or inflammatory response during pregnancy may be associated with schizophrenic psychosis in the adult offspring.

Risk of schizophrenia in adult offspring was examined in relation to maternal non-specific bacterial, respiratory or genital and reproductive infection during pregnancy. The results differed between studies, within and across infections, with an upper range of a two- to fivefold increased risk in all of the reports reviewed. With regard to particular infectious agents, evidence for HSV-2 and *T. gondii* was mixed, some studies reporting up to a twofold increased risk of schizophrenic psychosis. There was some indication that exposure to influenza, and other infections in general, during early stages of gestation may be more harmful. No evidence of an association was found between prenatal HSV-1 or CMV infection and adult psychotic illness. There was some suggestion that inflammatory cytokines may mediate risk of psychotic illness associated with prenatal infection. With regard to neurodevelopment, structural and functional brain abnormalities relevant to schizophrenia were reported in exposed cases.

Methodological issues that might have influenced the findings are discussed in the following sections.

Study populations

Much of the evidence on this topic comes from two US birth cohorts from which 15 reports were included (10 from the PDS cohort and five from the NCPP cohort). We observed overlap of participants between the reports of individual infectious exposures within each cohort. Five studies that reported associations with *T. gondii*, influenza, respiratory infection, genital/reproductive infection and IL-8 are based on the same 71 cases of SSD from the PDS cohort (Brown *et al*. 2000, 2004*a*, *b*, 2005; Babulas *et al*. 2006). Cases in four studies of structural and functional brain abnormalities related to prenatal infection also came from the same pool (Brown *et al*. 2009*a*, *b*, 2011; Ellman *et al*. 2010). A similar overlap of cases was noted in some studies from the NCPP cohort (Buka *et al*. 2001*a*,*b*, 2008; Ellman *et al*. 2009; Xiao *et al*. 2009).

It is possible that the individual infections were allocated randomly among the mothers. Alternatively, exposure to several infections in the same group of case mothers would suggest that related factors, such as lifestyle, may also be important. Indeed, in the NCPP cohort, the mother's sexual behaviour during pregnancy was found to be associated with HSV-2 infection and subsequent risk of schizophrenia in the adult offspring (Buka *et al*. 2008). Alternatively, or in addition, clusters of infections in a few mothers might suggest an innate susceptibility to infection that may itself be related to schizophrenia risk (discussed in biological plausibility). Regardless of the precise explanation for the associations, the validity of some the findings from the NCPP and PDS cohorts has been assisted by independent replications from large Danish datasets.

Because of the small sample size most studies could not address the issue of a sensitive period, with infection being harmful only during a particular stage of gestation. Sample sizes in studies of structural and functional brain abnormalities were also often small. None of them included any mediation model to properly explore the effects of prenatal infection on other indicators of schizophrenia.

Measurement of exposure

Selecting the criteria for exposure in serological studies can be difficult. For example, before deciding on cut-off values for antibodies to infectious agents, such as *T. gondii* or HSV, the prevalence of that infection in the population at the time and geographical region needs to be considered. Such considerations were given in some of the US studies and the Danish register-based studies.

IgG and IgM antibodies are both generated in response to infection (Janeway *et al*. 2001). IgM immunoglobulins are usually generated within a few days following systemic infection and are detectable for several months whereas IgG immunoglobulins are generated 1–3 weeks after initial infection and are detectable for several years (Buka *et al*. 2001*a*; Janeway *et al*. 2001). None of the studies of HSV-2 or *T. gondii* reported an increase in specific IgM antibodies, suggesting acute infections with these agents during pregnancy were unlikely.

Misclassification of exposure may be an issue in some studies. For example, in the Copenhagen Perinatal Cohort relatively broad categories of exposure were used (clinically diagnosed viral and bacterial infection) (Sorensen *et al*. 2009). Random misclassification would minimize the effect size by introducing bias results towards null.

The source of the prenatal sample may also be an issue. Studies from the NCPP and PDS cohorts used maternal serum samples that were stored at $-20\,^{\circ}C$ for >20 years. Degradation of antibodies and cytokines over time is possible; however, the authors reported that there was no evidence of freeze thawing

https://doi.org/10.1017/S0033291712000736 Published online by Cambridge University Press

(Buka *et al*. 2001*a*; Brown *et al*. 2004*a*). The Danish register-based studies used blood samples collected from neonates 5–7 days post-partum (Mortensen *et al*. 2007, 2010). However, it is highly likely that antibodies against HSV-2 or *T. gondii* in these samples represent foetal exposure to maternal infection rather than newly acquired infection after birth. Therefore, these can be regarded as valid measures of prenatal exposure to these infections.

Measurement of outcome

Broad outcomes were used in some cohorts (Table 2). Although studies from the NCPP cohort included both affective and non-affective psychosis, the outcome in the PDS cohort was non-affective psychosis only. This made examination of any links between an infection and specific diagnostic categories difficult. Differences in outcome definition may also account for discrepant findings between some of the studies from these two cohorts. The criteria for defining outcome also varied between studies. Typically, DSM was used in the US and ICD in the European studies.

Differences in methods of case ascertainment may have introduced bias in some studies. For example, in a study of maternal genital or reproductive infection, Babulas *et al*. (2006) reported that risk of SSD was higher in those where diagnosis was based on review of clinical notes as opposed to face-to-face interview.

Confounding and other methodological issues

Observed associations between schizophrenia in the adult offspring and maternal infections before and after pregnancy (Nielsen *et al*. 2011) and exposure to several infections in the same group of case mothers (PDS and NCPP cohort) may indicate possible confounding by other factors. Individuals who get one infection may be more likely to get others, so the infections might confound each other or all be markers for a third factor.

The characteristics of women who develop infections may be different from those who do not. Paternal infection was also reported to be associated with increased risk of schizophrenia in offspring (Nielsen *et al*. 2011). This indicates that poor living conditions and social adversity may be important confounding factors. However, most studies adjusted for social class in their analysis. In two large Danish studies the risk of schizophrenia in offspring associated with prenatal maternal HSV-2 or general infections was attenuated (although it remained statistically significant) after taking into account family history of psychosis (Mortensen *et al*. 2010; Nielsen *et al*. 2011). Nearly half of the studies were unable to adjust for this factor. It is possible that observed associations between various prenatal infections and schizophrenia in these studies may be partly confounded by family history of psychosis. However, as only 10–15% of patients with schizophrenia have a positive family history (Gottesman & Shields, 1982), confounding by this factor is unlikely to be the sole explanation for the observed associations. Attenuation of the effect size after adjusting for family history of psychosis in the Danish studies might reflect interaction. Indeed, one study reported evidence of interaction between infection and family history of psychosis using an additive model (Clarke *et al*. 2009). However, unlike the multiplicative model this approach is often more likely to yield a significant interaction in a large enough sample, and may therefore be less informative (Zammit *et al*. 2010). Therefore, these findings require replication.

Other methodological issues include the duration of follow-up and over-matching. The duration of follow-up was short in the Danish register-based studies and therefore their findings can be generalized to only early-onset cases of schizophrenia (Mortensen *et al*. 2007, 2010). As most studies matched their cases and controls on gender, they were not able to explore any gender difference in the effects of prenatal infection.

Biological plausibly of association

Mechanisms by which prenatal infections interfere with foetal development and contribute to risk of adult schizophrenia may include (i) direct interference with neurodevelopment by infectious agents or antibodies, (ii) induction of autoimmunity, (iii) the involvement of mediators of acute infection, (iv) reprogramming of the hypothalamic–pituitary–adrenal (HPA) axis, (v) activation of the innate immune system and effects of inflammatory cytokines, and (vi) interaction between host and microbe genome and/or environmental factors.

Maternal infection during pregnancy with neurotrophic agents, such as *T. gondii*, HSV and rubella, can interfere directly with foetal neurodevelopment. An extensive body of literature suggests that congenital infections with these agents can lead to mental retardation, cerebral hypoplasia, ventriculomegaly and other brain and behavioural abnormalities in the offspring (Remington *et al*. 2006). This is in line with findings from birth cohort studies reviewed here that reported structural and functional brain abnormalities relevant to schizophrenia in exposed cases. This is supported by evidence from animal model studies. Studies of prenatal maternal influenza (or immune activation) using experimental mouse models have reported increased ventricular and reduced brain

https://doi.org/10.1017/S0033291712000736 Published online by Cambridge University Press

volume, deficits in working memory, and reduced social and exploratory behaviour in offspring (Shi *et al*. 2003; Meyer & Feldon, 2010). In rhesus monkeys, prenatal maternal influenza has been reported to affect neural development in the offspring, reducing grey matter throughout most of the cortex and decreasing white matter in the parietal cortex (Short *et al*. 2010). It has been suggested that these brain alterations are likely to be permanent, given that they were still present at the monkey equivalent of older childhood, and thus might increase the likelihood of later behavioural pathology (Short *et al*. 2010).

None of the studies of *T. gondii* or HSV reviewed here used microbial culture, and the absence of IgM antibodies argues against acute infections with these agents during pregnancy. However, there is evidence that maternal IgG antibodies can cross the placenta and directly affect the foetal brain through molecular mimicry (Wright *et al*. 1999).

Infections can also induce autoimmunity, which may lead to further central nervous system (CNS) damage (Albert & Inman, 1999). It has been proposed that certain prenatal infections such as influenza may increase the risk of adult psychotic illness through induction of autoimmunity (Wright & Murray, 1993). Maternal neuronal autoantibodies against cerebellar Purkinje cells have been linked with classic neurodevelopmental disorders, such as autism (Dalton *et al*. 2003) and dyslexia (Vincent *et al*. 2002), in offspring. Increased autoimmunity including autoantibodies against ion channels, such as the voltage-gated potassium channel (VGKC), or the *N*-methyl-D-aspartate (NMDA) receptor is well documented in schizophrenia (Parthasarathi *et al*. 2006; Dalmau *et al*. 2011; Zandi *et al*. 2011). Search for other autoantibodies, in addition to microbe-specific antibodies, in prenatal maternal blood samples should help to elucidate to what extent prenatal infections are associated with autoimmunity.

Developmental effects of acute infections such as influenza may be mediated by hyperthermia and foetal hypoxia (Edwards, 1968; Milunsky *et al*. 1992; Cannon *et al*. 2002). The finding of increased risk of schizophrenia for maternal analgesic use during pregnancy in the Copenhagen cohort is in line with such mechanisms (Sorensen *et al*. 2009). Maternal analgesic use during pregnancy has also been linked with increased risk of childhood non-clinical psychotic symptoms (Gunawardana *et al*. 2011). However, it is yet to be established whether these are direct effect of the analgesics or of the infection that led to the use of analgesics.

Infection can increase foetal exposure to maternal glucocorticoids by inhibiting the placental enzyme 11-beta-hydroxysteroid dehydrogenase type 2 (Edwards *et al*. 1993; Johnstone *et al*. 2005; Seckl & Holmes, 2007; Meyer & Feldon, 2010). Excess glucocorticoids can reprogramme the HPA axis in the offspring, leading to either increased basal secretion or enhanced stress-related secretion of glucocorticoids later in life (Owen *et al*. 2005; Weinstock, 2008). Thus, increased basal cortisol levels observed in some cases of schizophrenia (Bradley & Dinan, 2010) may be related to maternal infections during pregnancy.

Prenatal maternal infection may explain common links between chronic physical and neuropsychiatric diseases of adult life. It has been suggested that people exposed to excess levels of glucocorticoids during pregnancy may be more likely to develop hypertension, hyperglycaemia, hyperinsulinaemia and hyperactivity of the HPA axis as adults (Barker *et al*. 1993; Seckl & Holmes, 2007). Similarly, activation of the HPA axis has been reported to be associated with increased blood pressure, insulin resistance, glucose intolerance and hyperlipidaemia (Reynolds *et al*. 2001). This might explain why schizophrenia patients have a higher risk of cardiovascular disease, diabetes and impaired glucose tolerance, which persists even after taking into account effects of antipsychotic drugs and lifestyle factors (Bushe & Holt, 2004; Curkendall *et al*. 2004).

As increased risk of psychosis has been observed for a diverse range of prenatal infections, it has been proposed that they may share a common pathway to exert pathogenic effects on the foetal brain. One such mechanism involves activation of the innate immune system and release of proinflammatory cytokines (Meyer *et al*. 2009). Reports from the NCPP and PDS cohorts suggest inflammatory cytokines may mediate risk of psychotic illness associated with prenatal infection (Buka *et al*. 2001*b*; Brown *et al*. 2004*b*).

A role of prenatal immune activation in schizophrenia is also supported by evidence from animal model studies (reviewed by Meyer & Feldon, 2010). Mouse models using pregnant females have included simulated viral or bacterial infection or direct injection with a cytokine (IL-6). These have been reported to produce intermediate phenotypes related to schizophrenia in the adult offspring. Some of these phenotypes, such as deficits in sensory gating and abnormal latent inhibition, have been shown to be reversible by treatment with clozapine, an antipsychotic (Smith *et al*. 2007). Cytokines can be neurotrophic and also neurotoxic depending on the developmental stage and condition (Garver *et al*. 2003). Elevated levels of cytokines during pregnancy have been reported to be associated with reduced cortical neuronal survival and reduced grey- and white-matter volume in animal studies (Meyer & Feldon, 2010; Short *et al*. 2010). Prenatal immune activation in animals has also been linked with

structural and functional alterations in the mesocorticolimbic dopaminergic system long before the onset of the full spectrum of psychosis-associated behavioural and cognitive abnormalities in adulthood (Meyer & Feldon, 2009).

Characteristics of both the microbial and human genome are likely to determine the pathological response to an infection to a large extent (Yolken & Torrey, 2008). For example, one study reported that infection with *T. gondii* type I, specifically, out of all three genotypes, was associated with increased risk of psychosis (Xiao *et al*. 2009). However, genetic determinants of human (host) response to infection include receptors, transcription factors, cytokines and other components of innate immunity (Yolken & Torrey, 2008).

It has been suggested that some genetic vulnerability to schizophrenia may be explained by genetic vulnerability to infection (Shi *et al*. 2009; Stefansson *et al*. 2009; Nielsen *et al*. 2011). Variations in the gene encoding IL-10 are reported to be associated with susceptibility to both CMV infection and schizophrenia (Bocchio Chiavetto *et al*. 2002; Hurme *et al*. 2003). More recently, a genome-wide association study (GWAS) of schizophrenia reported an association with a cytokine receptor gene, colony stimulating factor, receptor 2 alpha (*CSF2Rα*; Lencz *et al*. 2007). This gene is responsible for regulating important components of the innate immune system such as granulocytes and macrophages, which are the primary source of proinflammatory cytokines.

GWAS have also reported significant associations between schizophrenia and markers close to the major histocompatibility complex (MHC) region on chromosome 6 (Shi *et al*. 2009; Stefansson *et al*. 2009). This region includes several immunity-related genes and a histone gene cluster relevant to gene expression. This region contains genes involved in brain development, memory and cognition (Stefansson *et al*. 2009). Thus, increased risk of adult schizophrenia in the offspring for both paternal and maternal infection, as observed in a Danish sample (Nielsen *et al*. 2011), may reflect high genetic susceptibility to severe infection in future cases of schizophrenia. It is also possible that prenatal infection, by affecting gene expression or in the presence of pre-existing genetic vulnerabilities, can lead to a distinct or pathological immune response. This, in turn, may lead to CNS alterations, making these individuals susceptible to developing psychotic illness later in life.

Directions for future research

Studies using animal models could address whether or not there is a 'sensitive period' for vulnerability, an issue that must be resolved to understand the underlying biological mechanisms and to consider therapeutic interventions.

Duration of follow-up should cover at least the age of peak incidence of schizophrenia to make findings more generalizable. Effects of prenatal infections need to be examined in relation to specific psychopathology rather than broad diagnostic categories of schizophrenia or non-affective psychosis. Relationships between prenatal infection and well-established intermediate phenotypes of adult schizophrenia, such as childhood motor and cognitive development, should be explored using larger samples. The use of mediation models should be used to elucidate potential effects of prenatal infection on other antecedents of schizophrenia. Future studies should use triangulation of genetic information in addition to inflammatory cytokines and other immunological markers to elucidate effects of prenatal and early life infections on neurodevelopment and adult psychotic illness. Future investigations should also address to what extent genetic vulnerability to schizophrenia may be explained by genetic vulnerability to infection. Indeed, a new generation of general population birth cohorts, including the Norwegian Mother and Child Cohort Study (MoBa; Magnus *et al*. 2006), the Danish National Birth cohort (Olsen *et al*. 2001) and the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort (Golding *et al*. 2001) are currently conducting similar studies of neurodevelopmental outcomes. These cohorts have in-depth biological and other data and (for Norway and Denmark) large enough sample sizes to address issues such as mediation and mechanisms.

Strengths and limitations of this review

Our review is based on rigorous examination of robust population-based studies. Included studies reliably measured exposure at the individual level and defined outcome by contemporary ICD or DSM directives. Cases of psychosis were collected from general population registers or by a two-stage process (screening followed by a diagnostic interview). Individual studies also accounted for several confounding factors in design and analysis. These measures should increase both internal and external validity of the evidence. We included a variety of studies, for example those examining serological and clinically diagnosed infections, that used various epidemiological designs. We were not able to combine results of individual studies in a meta-analysis or carry out formal tests for publication bias. Meta-analyses were deemed unsuitable because of significant variation among studies on several important parameters. Nevertheless, to our

knowledge this is the most rigorously conducted independent appraisal of the population-based studies published on this topic to date.

Note

For supplementary material accompanying this paper, visit http://dx.doi.org/10.1017/S0033291712000736.

Acknowledgements

We are grateful to Dr C. Dalman for valuable comments on an earlier draft of this article and to Professors E. Susser and A. Brown for helpful discussions.

G.M.K. is supported by a grant from the Wellcome Trust (Clinical PhD Programme, grant no. 094790/Z/10/Z). P.B.J. is supported by the Wellcome Trust (095844/Z/11/Z and 088869/Z/09/Z) and the National Institute for Health Research (NIHR; RP-PG-0606-1335). The funding bodies had no further role in the study design, in the collection, analysis and interpretation of data, in the writing of the report, and in the decision to submit the paper for publication.

Declaration of Interest

None.

References

Albert LJ, Inman RD (1999). Molecular mimicry and autoimmunity. *New England Journal of Medicine* **341**, 2068–2074.

Babulas V, Factor-Litvak P, Goetz R, Schaefer CA, Brown AS (2006). Prenatal exposure to maternal genital and reproductive infections and adult schizophrenia. *American Journal of Psychiatry* **163**, 927–929.

Barker DJ, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS (1993). Fetal nutrition and cardiovascular disease in adult life. *Lancet* **341**, 938–941.

Bocchio Chiavetto L, Boin F, Zanardini R, Popoli M, Michelato A, Bignotti S, Tura GB, Gennarelli M (2002). Association between promoter polymorphic haplotypes of interleukin-10 gene and schizophrenia. *Biological Psychiatry* **51**, 480–484.

Bradley AJ, Dinan TG (2010). A systematic review of hypothalamic-pituitary-adrenal axis function in schizophrenia: implications for mortality. *Journal of Psychopharmacology* **24**, 91–118.

Brown AS, Begg MD, Gravenstein S, Schaefer CA, Wyatt RJ, Bresnahan M, Babulas VP, Susser ES (2004*a*). Serologic evidence of prenatal influenza in the etiology of schizophrenia. *Archives of General Psychiatry* **61**, 774–780.

Brown AS, Cohen P, Harkavy-Friedman J, Babulas V, Malaspina D, Gorman JM, Susser ES (2001). A.E. Bennett Research Award. Prenatal rubella, premorbid abnormalities, and adult schizophrenia. *Biological Psychiatry* **49**, 473–486.

Brown AS, Deicken RF, Vinogradov S, Kremen WS, Poole JH, Penner JD, Kochetkova A, Kern D, Schaefer CA (2009*a*). Prenatal infection and cavum septum pellucidum in adult schizophrenia. *Schizophrenia Research* **108**, 285–287.

Brown AS, Derkits EJ (2010). Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. *American Journal of Psychiatry* **167**, 261–280.

Brown AS, Hooton J, Schaefer CA, Zhang H, Petkova E, Babulas V, Perrin M, Gorman JM, Susser ES (2004*b*). Elevated maternal interleukin-8 levels and risk of schizophrenia in adult offspring. *American Journal of Psychiatry* **161**, 889–895.

Brown AS, Schaefer CA, Quesenberry Jr. CP, Liu L, Babulas VP, Susser ES (2005). Maternal exposure to toxoplasmosis and risk of schizophrenia in adult offspring. *American Journal of Psychiatry* **162**, 767–773.

Brown AS, Schaefer CA, Quesenberry Jr. CP, Shen L, Susser ES (2006). No evidence of relation between maternal exposure to herpes simplex virus type 2 and risk of schizophrenia? *American Journal of Psychiatry* **163**, 2178–2180.

Brown AS, Schaefer CA, Wyatt RJ, Goetz R, Begg MD, Gorman JM, Susser ES (2000). Maternal exposure to respiratory infections and adult schizophrenia spectrum disorders: a prospective birth cohort study. *Schizophrenia Bulletin* **26**, 287–195.

Brown AS, Vinogradov S, Kremen WS, Poole JH, Bao Y, Kern D, McKeague IW (2011). Association of maternal genital and reproductive infections with verbal memory and motor deficits in adult schizophrenia. *Psychiatry Research* **188**, 179–186.

Brown AS, Vinogradov S, Kremen WS, Poole JH, Deicken RF, Penner JD, McKeague IW, Kochetkova A, Kern D, Schaefer CA (2009*b*). Prenatal exposure to maternal infection and executive dysfunction in adult schizophrenia. *American Journal of Psychiatry* **166**, 683–690.

Buka SL, Cannon TD, Torrey EF, Yolken RH (2008). Maternal exposure to herpes simplex virus and risk of psychosis among adult offspring. *Biological Psychiatry* **63**, 809–815.

Buka SL, Tsuang MT, Torrey EF, Klebanoff MA, Bernstein D, Yolken RH (2001*a*). Maternal infections and subsequent psychosis among offspring. *Archives of General Psychiatry* **58**, 1032–1037.

Buka SL, Tsuang MT, Torrey EF, Klebanoff MA, Wagner RL, Yolken RH (2001*b*). Maternal cytokine levels during pregnancy and adult psychosis. *Brain Behaviour and Immunity* **15**, 411–420.

Bushe C, Holt R (2004). Prevalence of diabetes and impaired glucose tolerance in patients with schizophrenia. *British Journal of Psychiatry* **184** (Suppl. 47), S67–S71.

Cannon M, Jones PB, Murray RM (2002). Obstetric complications and schizophrenia: historical and meta-analytic review. *American Journal of Psychiatry* **159**, 1080–1092.

Clarke MC, Tanskanen A, Huttunen M, Whittaker JC, Cannon M (2009). Evidence for an interaction between familial liability and prenatal exposure to infection in the

causation of schizophrenia. *American Journal of Psychiatry* **166**, 1025–1030.

Curkendall SM, Mo J, Glasser DB, Rose Stang M, Jones JK (2004). Cardiovascular disease in patients with schizophrenia in Saskatchewan, Canada. *Journal of Clinical Psychiatry* **65**, 715–720.

Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R (2011). Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurology* **10**, 63–74.

Dalton P, Deacon R, Blamire A, Pike M, McKinlay I, Stein J, Styles P, Vincent A (2003). Maternal neuronal antibodies associated with autism and a language disorder. *Annals of Neurology* **53**, 533–537.

Edwards CR, Benediktsson R, Lindsay RS, Seckl JR (1993). Dysfunction of placental glucocorticoid barrier: link between fetal environment and adult hypertension? *Lancet* **341**, 355–357.

Edwards MJ (1968). Congenital malformations in the rat following induced hyperthermia during gestation. *Teratology* **1**, 173–177.

Ellman LM, Deicken RF, Vinogradov S, Kremen WS, Poole JH, Kern DM, Tsai WY, Schaefer CA, Brown AS (2010). Structural brain alterations in schizophrenia following fetal exposure to the inflammatory cytokine interleukin-8. *Schizophrenia Research* **121**, 46–54.

Ellman LM, Yolken RH, Buka SL, Torrey EF, Cannon TD (2009). Cognitive functioning prior to the onset of psychosis: the role of fetal exposure to serologically determined influenza infection. *Biological Psychiatry* **65**, 1040–1047.

Garver DL, Tamas RL, Holcomb JA (2003). Elevated interleukin-6 in the cerebrospinal fluid of a previously delineated schizophrenia subtype. *Neuropsychopharmacology* **28**, 1515–1520.

Golding J, Pembrey M, Jones R (2001). ALSPAC – the Avon Longitudinal Study of Parents and Children. I. Study methodology. *Paediatric and Perinatal Epidemiology* **15**, 74–87.

Gottesman II, Shields J (1982). *Schizophrenia: The Epigenetic Puzzle*. Cambridge University Press: New York.

Gunawardana L, Zammit S, Lewis G, Gunnell D, Hollis C, Wolke D, Harrison G (2011). Examining the association between maternal analgesic use during pregnancy and risk of psychotic symptoms during adolescence. *Schizophrenia Research* **126**, 220–225.

Hurme M, Haanpaa M, Nurmikko T, Wang XY, Virta M, Pessi T, Kilpinen S, Hulkkonen J, Helminen M (2003). IL-10 gene polymorphism and herpesvirus infections. *Journal of Medical Virology* **70** (Suppl. 1), S48–S50.

Janeway CA, Travers P, Walport M, Shlomchik MJ (2001). *Immunobiology: The Immune System in Health and Disease*. Garland Science: New York.

Johnstone JF, Bocking AD, Unlugedik E, Challis JR (2005). The effects of chorioamnionitis and betamethasone on 11beta hydroxysteroid dehydrogenase types 1 and 2 and the glucocorticoid receptor in preterm human placenta. *Journal of the Society for Gynecologic Investigation* **12**, 238–245.

Jones P, Rodgers B, Murray R, Marmot M (1994). Child development risk factors for adult schizophrenia in the British 1946 birth cohort. *Lancet* **344**, 1398–1402.

Khandaker GM, Barnett JH, White IR, Jones PB (2011). A quantitative meta-analysis of population-based studies of premorbid intelligence and schizophrenia. *Schizophrenia Research* **132**, 220–227.

Lencz T, Morgan TV, Athanasiou M, Dain B, Reed CR, Kane JM, Kucherlapati R, Malhotra AK (2007). Converging evidence for a pseudoautosomal cytokine receptor gene locus in schizophrenia. *Molecular Psychiatry* **12**, 572–580.

Magnus P, Irgens LM, Haug K, Nystad W, Skjaerven R, Stoltenberg C (2006). Cohort profile: the Norwegian Mother and Child Cohort Study (MoBa). *International Journal of Epidemiology* **35**, 1146–1150.

Mednick SA, Machon RA, Huttunen MO, Bonett D (1988). Adult schizophrenia following prenatal exposure to an influenza epidemic. *Archives of General Psychiatry* **45**, 189–192.

Menninger KA (1994). Influenza and schizophrenia. An analysis of post-influenzal 'dementia precox,' as of 1918, and five years later further studies of the psychiatric aspects of influenza. 1926. *American Journal of Psychiatry* **151**, 182–187.

Meyer U, Feldon J (2009). Prenatal exposure to infection: a primary mechanism for abnormal dopaminergic development in schizophrenia. *Psychopharmacology* (*Berlin*) **206**, 587–602.

Meyer U, Feldon J (2010). Epidemiology-driven neurodevelopmental animal models of schizophrenia. *Progress in Neurobiology* **90**, 285–326.

Meyer U, Feldon J, Yee BK (2009). A review of the fetal brain cytokine imbalance hypothesis of schizophrenia. *Schizophrenia Bulletin* **35**, 959–972.

Milunsky A, Ulcickas M, Rothman KJ, Willett W, Jick SS, Jick H (1992). Maternal heat exposure and neural tube defects. *Journal of the American Medical Association* **268**, 882–885.

Mortensen PB, Norgaard-Pedersen B, Waltoft BL, Sorensen TL, Hougaard D, Torrey EF, Yolken RH (2007). *Toxoplasma gondii* as a risk factor for early-onset schizophrenia: analysis of filter paper blood samples obtained at birth. *Biological Psychiatry* **61**, 688–693.

Mortensen PB, Pedersen CB, Hougaard DM, Norgaard-Petersen B, Mors O, Borglum AD, Yolken RH (2010). A Danish National Birth Cohort study of maternal HSV-2 antibodies as a risk factor for schizophrenia in their offspring. *Schizophrenia Research* **122**, 257–263.

Murray RM, Lewis SW (1987). Is schizophrenia a neurodevelopmental disorder? *British Medical Journa* (*Clinical Research Edition*) **295**, 681–682.

Nielsen PR, Laursen TM, Mortensen PB (2011). Association between parental hospital-treated infection and the risk of schizophrenia in adolescence and early adulthood. *Schizophrenia Bulletin*. Published online 20 October 2011. doi:10.1093/schbul/sbr149.

Olsen J, Melbye M, Olsen SF, Sorensen TI, Aaby P, Andersen AM, Taxbol D, Hansen KD, Juhl M, Schow TB,

Sorensen HT, Andresen J, Mortensen EL, Olesen AW, Sondergaard C (2001). The Danish National Birth Cohort – its background, structure and aim. *Scandinavian Journal of Public Health* **29**, 300–307.

Owen D, Andrews MH, Matthews SG (2005). Maternal adversity, glucocorticoids and programming of neuroendocrine function and behaviour. *Neuroscience and Biobehavioural Reviews* **29**, 209–26.

Parthasarathi UD, Harrower T, Tempest M, Hodges JR, Walsh C, McKenna PJ, Fletcher PC (2006). Psychiatric presentation of voltage-gated potassium channel antibody-associated encephalopathy. Case report. *British Journal of Psychiatry* **189**, 182–183.

Remington JS, Klein JO, Wilson GB, Baker CJ (2006). *Infectious Diseases of the Fetus and Newborn Infant*. Elsevier Saunders: Philadelphia.

Reynolds RM, Walker BR, Syddall HE, Andrew R, Wood PJ, Whorwood CB, Phillips DI (2001). Altered control of cortisol secretion in adult men with low birth weight and cardiovascular risk factors. *Journal of Clinical Endocrinology and Metabolism* **86**, 245–250.

Seckl JR, Holmes MC (2007). Mechanisms of disease: glucocorticoids, their placental metabolism and fetal 'programming' of adult pathophysiology. *Nature Clinical Practice. Endocrinology and Metabolism* **3**, 479–488.

Selten JP, Frissen A, Lensvelt-Mulders G, Morgan VA (2010). Schizophrenia and 1957 pandemic of influenza: meta-analysis. *Schizophrenia Bulletin* **36**, 219–228.

Shi J, Levinson DF, Duan J, Sanders AR, Zheng Y, Pe'er I, Dudbridge F, Holmans PA, Whittemore AS, Mowry BJ, Olincy A, Amin F, Cloninger CR, Silverman JM, Buccola NG, Byerley WF, Black DW, Crowe RR, Oksenberg JR, Mirel DB, Kendler KS, Freedman R, Gejman PV (2009). Common variants on chromosome 6p22.1 are associated with schizophrenia. *Nature* **460**, 753–757.

Shi L, Fatemi SH, Sidwell RW, Patterson PH (2003). Maternal influenza infection causes marked behavioral and pharmacological changes in the offspring. *Journal of Neuroscience* **23**, 297–302.

Short SJ, Lubach GR, Karasin AI, Olsen CW, Styner M, Knickmeyer RC, Gilmore JH, Coe CL (2010). Maternal influenza infection during pregnancy impacts postnatal brain development in the rhesus monkey. *Biological Psychiatry* **67**, 965–973.

Smith SE, Li J, Garbett K, Mirnics K, Patterson PH (2007). Maternal immune activation alters fetal brain development through interleukin-6. *Journal of Neuroscience* **27**, 10695–10702.

Sorensen HJ, Mortensen EL, Reinisch JM, Mednick SA (2009). Association between prenatal exposure to bacterial infection and risk of schizophrenia. *Schizophrenia Bulletin* **35**, 631–637.

Stefansson H, Ophoff RA, Steinberg S, Andreassen OA, Cichon S, Rujescu D, Werge T, Pietilainen OP, Mors O, Mortensen PB, Sigurdsson E, Gustafsson O, Nyegaard M, Tuulio-Henriksson A, Ingason A, Hansen T, Suvisaari J, Lonnqvist J, Paunio T, Borglum AD, Hartmann A, Fink-Jensen A, Nordentoft M, Hougaard D, Norgaard-Pedersen B, Bottcher Y, Olesen J, Breuer R, Moller HJ, Giegling I, Rasmussen HB, Timm S, Mattheisen M, Bitter I, Rethelyi JM, Magnusdottir BB, Sigmundsson T, Olason P, Masson G, Gulcher JR, Haraldsson M, Fossdal R, Thorgeirsson TE, Thorsteinsdottir U, Ruggeri M, Tosato S, Franke B, Strengman E, Kiemeney LA, Melle I, Djurovic S, Abramova L, Kaleda V, Sanjuan J, de Frutos R, Bramon E, Vassos E, Fraser G, Ettinger U, Picchioni M, Walker N, Toulopoulou T, Need AC, Ge D, Yoon JL, Shianna KV, Freimer NB, Cantor RM, Murray R, Kong A, Golimbet V, Carracedo A, Arango C, Costas J, Jonsson EG, Terenius L, Agartz I, Petursson H, Nothen MM, Rietschel M, Matthews PM, Muglia P, Peltonen L, St Clair D, Goldstein DB, Stefansson K, Collier DA (2009). Common variants conferring risk of schizophrenia. *Nature* **460**, 744–747.

Susser E (1999). Life course cohort studies of schizophrenia. *Psychiatric Annals* **29**, 161–165.

Susser E, Buka S, Schaefer CA, Andrews H, Cirillo PM, Factor-Litvak P, Gillman M, Goldstein JM, Ivey Henry P, Lumey LH, McKeague IW, Michels KB, Terry MB, Cohn BA; for the EDAH Team (2011). The Early Determinants of Adult Health Study. *Journal of Developmental Origins of Health and Disease* **2**, 311–321.

Susser ES, Schaefer CA, Brown AS, Begg MD, Wyatt RJ (2000). The design of the Prenatal Determinants of Schizophrenia Study. *Schizophrenia Bulletin* **26**, 257–273.

van dan Berg BJ, Christianson RE, Oeschsli FW (1988). The California Child Health and Development Studies of the School of Public Health, University of California, Berkeley. *Pediatric and Perinatal Epidemiology* **2**, 265–282.

Vincent A, Deacon R, Dalton P, Salmond C, Blamire AM, Pendlebury S, Johansen-Berg H, Rajogopalan B, Styles P, Stein J (2002). Maternal antibody-mediated dyslexia? Evidence for a pathogenic serum factor in a mother of two dyslexic children shown by transfer to mice using behavioural studies and magnetic resonance spectroscopy. *Journal of Neuroimmunology* **130**, 243–247.

von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative (2007). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* **370**, 1453–1457.

Weinberger DR (1987). Implications of normal brain development for the pathogenesis of schizophrenia. *Archives of General Psychiatry* **44**, 660–669.

Weinstock M (2008). The long-term behavioural consequences of prenatal stress. *Neuroscience and Biobehavioural Reviews* **32**, 1073–1086.

Wright P, Murray RM (1993). Schizophrenia: prenatal influenza and autoimmunity. *Annals of Medicine* **25**, 497–502.

Wright P, Takei N, Murray RM, Sham P (1999). Seasonality, prenatal influenza exposure, and schizophrenia. In *Prenatal Exposures in Schizophrenia* (ed. E. Susser, A. S. Brown and J. M. Gorman), pp. 89–112. American Psychiatric Press: Washington DC.

Xiao J, Buka SL, Cannon TD, Suzuki Y, Viscidi RP, Torrey EF, Yolken RH (2009). Serological pattern consistent with infection with type I *Toxoplasma gondii* in mothers and risk of psychosis among adult offspring. *Microbes and Infection* **11**, 1011–1018.

Yolken RH, Torrey EF (2008). Are some cases of psychosis caused by microbial agents? A review of the evidence. *Molecular Psychiatry* **13**, 470–479.

Zammit S, Lewis G, Dalman C, Allebeck P (2010). Examining interactions between risk factors for psychosis. *British Journal of Psychiatry* **197**, 207–211.

Zandi MS, Irani SR, Lang B, Waters P, Jones PB, McKenna P, Coles AJ, Vincent A, Lennox BR (2011). Disease-relevant autoantibodies in first episode schizophrenia. *Journal of Neurology* **258**, 686–688.