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Maternal exposure to sexually transmitted infections and schizophrenia among offspring

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Abstract

Animal models and epidemiologic studies suggest that prenatal maternal infection, and sexually transmitted infection (STI) in particular, is associated with an increased risk of schizophrenia in the offspring. However, findings from prior research studies on common infections, including herpes simplex virus type 2 (HSV-2) and *Chlamydia trachomatis* (*C. trachomatis*) have been inconsistent. To investigate these associations, we conducted a case-control study nested in the population-based Finnish Prenatal Study of Schizophrenia. Using linked national registries, 963 cases with schizophrenia (ICD-10 F20) or schizoaffective disorder (ICD-10 F25), and 963 matched controls were identified from among all persons born between 1983-1998 in Finland. HSV-2 IgG antibody levels were quantified in archived maternal serum samples drawn during pregnancy. Mothers of 16.4% of cases versus 12.6% of controls were HSV-2 seropositive. Mean levels of maternal HSV-2 IgG were marginally higher among cases than controls (index values of 0.98 versus 0.86; p=0.06). The unadjusted odds ratio (OR) of maternal HSV-2 IgG seropositivity was 1.33 (95% confidence interval (CI) = 1.03-1.72, p=0.03). Following adjustment for covariates, the relationship was attenuated (OR=1.22, CI=0.93-1.60; p=0.14). In an exploratory analysis of another STI, *C. trachomatis* antibodies were measured in a subsample of 207 case-control pairs

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Contributors:

The study was conceptualized by A.S. Brown, A. Sourander, and K. Cheslack-Postava. J. Huttunen, H.M. Surcel, and A. Sourander contributed to the data collection and A. Suominen conducted the statistical analyses. The results were interpreted and the manuscript drafted by K. Cheslack-Postava, A.S. Brown, and R. Chudal. A. Sourander and H.M. Surcel also contributed to the interpretation of the results. All authors contributed to and have approved the final manuscript.

Conflict of interest:

The authors declare that they have no conflict of interest.

drawn from the cohort. The proportions of subjects that were seropositive and the mean levels of *C. trachomatis* antibodies were similar for cases and controls. This study does not support a strong association of HSV-2 or *C. trachomatis* IgG antibodies in maternal serum during early to mid-gestation with the development of schizophrenia in the offspring.

Keywords

schizophrenia; HSV-2; chlamydia; prenatal infection; epidemiology

1. Introduction

Epidemiologic studies and animal models of maternal immune activation provide evidence that prenatal maternal infection is a risk factor for the development of schizophrenia in the offspring (Brown and Patterson, 2011). Specific infectious agents including rubella (Brown et al., 2001), influenza (Brown et al., 2004), and *Toxoplasma gondii* (Brown et al., 2005; Mortensen et al., 2007) have been linked to schizophrenia. Maternal diagnosis with genital and reproductive infections during the periconceptional period, as reported in obstetric records, was associated with a fivefold increased risk of schizophrenia among members of a cohort born between 1959-1966 in California (Babulas et al., 2006). The infections included endometritis, cervicitis, pelvic inflammatory disease, vaginitis, syphilis, condylomata, “venereal disease,” and gonorrhea, but whether the association was attributable to particular pathogens was not determined. Therefore, investigating maternal exposure to specific common genital and reproductive infections, such as those that are sexually transmitted, may yield additional risk factors for schizophrenia. Two of the most common sexually transmitted infections (STIs) are herpes simplex virus type 2 (HSV-2) and *Chlamydia trachomatis* (*C. trachomatis*).

HSV-2 infection during pregnancy has known teratogenic effects, including on cognitive development (Adams Waldorf and McAdams, 2013), and has been investigated with respect to risk for schizophrenia. However, results of these studies have been inconsistent, with some (Buka et al., 2008; Buka et al., 2001; Mortensen et al., 2010) reporting positive associations, and others (Blomstrom et al., 2012; Brown et al., 2006; Mortensen et al., 2007) finding no relationship. This may be due in part to low participation rates (Blomstrom et al., 2012); the use of neonatal biosamples in some studies (Blomstrom et al., 2012; Mortensen et al., 2007; Mortensen et al., 2010) versus maternal biosamples in others (Brown et al., 2006; Buka et al., 2008; Buka et al., 2001); and limited numbers of cases (Blomstrom et al., 2012; Brown et al., 2006; Buka et al., 2001). The only prior studies that examined prenatal maternal serum samples (Brown et al., 2006; Buka et al., 2008; Buka et al., 2001) used specimens collected late in pregnancy and had modest sample sizes.

C. trachomatis is the most common bacterial STI in the U.S. (Darville, 2006) and has been associated with adverse pregnancy outcomes including spontaneous abortion, stillbirth and preterm birth, in addition to conjunctivitis and respiratory infection in the neonate (Mardh, 2002). To our knowledge, only one small study has previously examined whether the presence of *C. trachomatis* antibodies in maternal prenatal serum is related to offspring

schizophrenia diagnosis, finding no significant difference between cases and controls (Buka et al., 2001).

In order to overcome the limitations of the previous studies of HSV-2 and schizophrenia to date, we used archived maternal serum samples drawn during early to mid-gestation from the population-based Finnish Prenatal Study of Schizophrenia (FIPS-S), a large, national birth cohort study. For this purpose, we measured IgG antibody specific to HSV-2 in maternal serum specimens drawn during pregnancy for 963 case-control pairs. Measures for maternal *C. trachomatis* IgG were also obtained, though in a limited subsample of 207 case-control pairs, due to funding constraints. Nonetheless, this was a potentially important exploratory analysis, given that this common STI has been investigated in only a limited way in relation to schizophrenia.

2. Methods

2.1. Study Description

Study subjects were identified through the Finnish Prenatal Study of Schizophrenia (FIPS-S), a nested case-control study based on a national cohort of all births in Finland from 1983-1998, and followed up until 2009. The data used in this study were derived from national registries, the Finnish Hospital Discharge Register (FHDR), the Finnish Medical Birth Register (FMBR), and the Finnish Central Population Register (CPR), and Statistics Finland (described below), which were linked using the unique personal identity codes given to every Finnish resident.

The FHDR is maintained by the National Institute of Health and Welfare, and includes all public and private inpatient diagnoses since January 1, 1967, and outpatient diagnoses since January 1, 1998. Diagnoses in the FHDR are based on the International Classification of Diseases and Related Health Problems (ICD). Previous validation studies have reported that 87% (Arajarvi et al., 2005) and 93% (Makikyro et al., 1998) of patients with register-based schizophrenia spectrum diagnoses also met criteria for schizophrenia spectrum disorders following research reviews of medical records.

The FMBR is also maintained by the National Institute of Health and Welfare, and includes comprehensive data on the pre-, peri-, and neonatal periods up to seven days following delivery for all births in Finland. It was established in 1987. The FCPR contains basic information about Finnish citizens and foreign citizens residing permanently in Finland, including name, personal identity code, address, municipality of residence, country and date of immigration/emigration, mother language, family relations and date of birth and death. A fourth registry, Statistics Finland, was used to identify the level of urbanicity of birth locations.

Serum samples were drawn for the purpose of prenatal screening from over 98% of the mothers of cohort members during early to mid-pregnancy, and subsequently archived at −25° C in a single, centralized repository. These samples were linked to the other registries using the personal identity codes.

2.2. Identification of Subjects

A total of 1,514 cases with a diagnosis of schizophrenia (ICD-10 F20) or schizoaffective disorder (ICD-10 F25) (henceforth referred to collectively as "schizophrenia") occurring through 2009 were identified. For each case, one control was randomly selected from the cohort, and matched on date of birth (+/− one month), sex, and having been alive and residing in Finland at the time of the case diagnosis. Control subjects were required to be without diagnoses of schizophrenia, other non-affective psychotic disorders, or bipolar disorder at the time of case diagnosis. For HSV-2, all case-control pairs with adequate quantities of sera for analysis were assayed. Because the *C. trachomatis* analysis was exploratory, a limited sample of case-control pairs was selected at random from those with sera available.

2.3. Laboratory Analyses

IgG class antibodies to HSV-2 in sera were measured by HerpeSelect® 2 ELISA (Focus Diagnostics, Cypress, California, USA). The sensitivity and specificity of the assay are 96.1% and 97.0%, respectively. The results are expressed as index values relative to the cut-off calibrator, calculated by dividing the specimen optical density (OD) values by the mean of the cut-off calibrator absorbance values. The index values are interpreted as follows: >1.10, positive; ≥0.90 and ≤1.10, equivocal; <0.90, negative. *C. trachomatis* specific IgG antibodies were analyzed using ELISA kits (AniLabsystems Ltd, Vantaa, Finland). A peptide-based EIA test is considered species-specific with minimal cross-reactivity with other *Chlamydia* species. The reproducibility of the test is high (SD 0.061, coefficient of variation 4.9%). Results are expressed as absorbance of the sample, with absorbance values interpreted as follows: ≥1.0, positive; >0.6 and <1.0, equivocal; ≤0.6, negative.

2.4. Covariates

Covariates were selected for inclusion based on potential associations with schizophrenia and with maternal prenatal IgG seropositivity to HSV-2 and *C. trachomatis*. These variables included maternal age, paternal age, maternal parity, maternal education, paternal education, maternal or parental history of psychiatric disorders (schizophrenia, non-affective psychosis, affective disorders, any psychiatric disorder), gestational age, gestational week of blood draw, multiple versus singleton birth, municipality of birth, province of birth, and maternal immigration status. Covariates were categorized as shown in Table 1.

2.5. Statistical Analysis

Bivariate associations of the covariates with: a) schizophrenia, and with b) HSV-2 and *C. trachomatis* positivity among the controls were examined using χ^2 or t-tests. First, preliminary analyses examining the association between antigen-specific IgG and schizophrenia diagnosis were conducted using all observations. Mean levels of HSV-2 and *C. trachomatis* IgG were compared between cases and controls using paired t-tests, and the unadjusted distributions of seropositivity status (positive, equivocal, negative) were compared between cases and controls using conditional logistic regression for matched pairs.

The main analyses focused on the 98.1% of observations that were unambiguously seropositive or negative for maternal HSV-2 IgG. The rationale for excluding observations with equivocal seropositivity from these analyses was to reduce potential bias due to misclassification of the exposure. HSV-2 IgG was considered as a dichotomous variable (positive versus negative) and as a continuous variable (log-transformed due to the skewed distribution). For the analysis of HSV-2 IgG as a continuous variable, seronegative observations were set to a value of 0 because the ELISA measures are not interpretable for seronegative samples. Conditional logistic regression models were fit both without, and following adjustment for potential confounders. Covariates were considered potential confounders if they were associated with both schizophrenia and HSV-2 seropositivity, and were not in a potential causal pathway between the two (Greenland and Rothman, 2008). We did not consider covariates hypothesized to act as potential mediators because by definition they cannot be confounders. The association of covariates with schizophrenia and HSV-2 seropositivity was evaluated based on criteria of $p<0.05$ and $p<0.10$ in separate models. To determine whether there was any heterogeneity of association by case characteristics, models were fit stratified by sex, case diagnosis (F20 versus F25), and case age at first treatment (below versus at or above the median). Stratum specific odds ratios were compared using a test of heterogeneity appropriate for estimates from distinct populations (Altman and Bland, 2003). To determine whether there was evidence for interaction with covariates, models were fit including product terms between HSV-2 measures and, respectively, indicators for categories of urbanicity or for any parental history of psychiatric diagnosis. Interaction models were fit using both HSV-2 seropositivity and HSV-2 levels as the measures of interest. The statistical significance of the interaction terms in the models was assessed using Wald and likelihood ratio tests and stratum-specific odds ratios were computed by parental psychiatric diagnosis and by level of urbanicity. Because there was no preliminary evidence for an association between schizophrenia and *C. trachomatis* IgG, no adjusted models were fit for this exposure.

3. Results

Characteristics of cases with schizophrenia and of controls are shown in Table 1. Fathers of cases were significantly older and more likely to be of the lowest or highest education levels relative to those of controls. All categories of psychiatric diagnosis were more common among both mothers and fathers of cases. Additionally, cases were more likely to have been born in urban areas and in Southern Finland.

Comparisons of the covariates between maternal HSV-2 IgG seropositive and seronegative control subjects and between maternal *C. trachomatis* IgG seropositive and seronegative control subjects are shown in Table 2. Maternal HSV-2 seropositivity was associated with older maternal and paternal age, and was more frequent among males and those born in Southern Finland province. Parental history of schizophrenia or non-affective psychosis was also marginally ($p=0.07$) more frequent among maternal HSV-2 IgG seropositive versus seronegative control subjects. Maternal *C. trachomatis* IgG seropositivity was significantly associated only with municipality of birth ($p<0.05$), with seropositive mothers more likely to be of urban residence.

Mean levels of HSV-2 IgG were marginally higher among cases than controls (index values of 0.98 versus 0.86; p=0.06). 16.4% of cases versus 12.6% of controls were seropositive (Table 3).

The association of maternal HSV-2 IgG with schizophrenia was examined among the subjects with non-equivocal HSV-2 antibody measurements, using both categorical and continuous (log-transformed) measures of this exposure (Table 3). In the analysis of HSV-2 as a categorical measure, the OR for being HSV-2 seropositive versus seronegative was 1.33 (95% CI=1.03-1.72; p=0.03). However, upon adjustment for paternal age and province of birth, the association was attenuated and became non-significant (OR=1.22, 95% CI=0.93-1.60; p=0.14). Adjustment for paternal age individually (OR=1.29, 95% CI=0.99-1.69; p=0.06), or province of birth individually (OR=1.25, 95% CI=0.96-1.62; p=0.10), also rendered the association non-significant, though there were statistical trends for associations. In the analysis of HSV-2 IgG as a continuous measure, the OR for each one unit increase in log-transformed HSV-2 IgG level was 1.21 (95% CI=0.99-1.47; p=0.06). This association also was attenuated and non-significant (OR=1.12, 95% CI=0.91-1.38; p=0.29) following adjustment for paternal age and province of birth. Further adjustment for parental schizophrenia diagnosis gave similar results (Table 3). Examination of the covariates and exposure variables in each of these models revealed low correlation ($|r| <= 0.1$) between all variables, indicating that collinearity did not influence the results. No evidence for significant heterogeneity in the HSV-2-schizophrenia association by subject sex, case diagnosis, or case age at first treatment below or above the median was observed ($p>0.10$ for all tests of heterogeneity). Interaction terms between HSV-2 measures of seropositivity and IgG level and urbanicity or parental history of psychiatric diagnosis did not contribute significantly to the models ($p\geq0.40$). None of the estimates of association for HSV-2 with schizophrenia within strata of history of parental psychiatric diagnosis or urbanicity were statistically significant (Supplemental Table 1).

Neither *C. trachomatis* IgG levels nor seropositivity status differed between cases and controls. Relative to subjects who were seronegative for *C. trachomatis* antibodies, those who were seropositive had an unadjusted OR of 1.04 (95% CI = 0.59-1.81; p=0.88) for schizophrenia. Due to the lack of preliminary evidence for an association between schizophrenia and *C. trachomatis* IgG, adjusted models were not fit for this exposure.

4. Discussion

To our knowledge, this is the largest study to date on the question of whether maternal HSV-2, or *C. trachomatis* seroprevalence or IgG antibody levels, are associated with schizophrenia in offspring, and the first to measure these antibodies in maternal serum samples drawn during early to mid-gestation. We did not find evidence to support strong or significant associations between these biomarkers of either pathogen during early to mid-gestation with the later development of schizophrenia.

The lack of a significant association between prenatal maternal HSV-2 infection and schizophrenia is consistent with previous studies from Denmark (Mortensen et al., 2007) and Sweden (Blomstrom et al., 2012) that used neonatal dried blood spots, and with a study

from California that examined maternal serum from late pregnancy (Brown et al., 2006). It is in contrast, however, with three previous studies that demonstrated positive associations between maternal HSV-2 IgG and schizophrenia/other psychoses. The first of these was a Danish case-control study using newborn dried blood spots (Mortensen et al., 2010), while the second and third were case-control studies of psychotic disorders (mostly schizophrenia-related psychoses) in a birth cohort from the USA, which utilized serum samples taken from mothers at the end of pregnancy (Buka et al., 2008; Buka et al., 2001).

Due to the differences in timing of samples from which maternal antibodies were measured, the results of this study are not necessarily directly comparable to prior studies. However, given the low rates among Finnish women for seroconversion for HSV-2 (i.e. 0% (Alanen et al., 2005) to 0.6% (Arvaja et al., 1999) during pregnancy) and for *C. trachomatis* (maximum of 2.6% per year among women under age 23, with lower rates in older age groups) (Lyytikainen et al., 2008), new infections would account for only a minor proportion of all seroprevalence for each of these pathogens. Hence, we would not have expected the timing of the sample draw (early versus late pregnancy) to have an effect on the results.

It is possible that studies differed in the degree to which results were impacted by residual confounding. In our study, an initially significant association between schizophrenia and HSV-2 seropositivity became attenuated and non-significant after adjustment for paternal age, province of birth, and parental schizophrenia diagnosis, although there was a statistical trend for an association when adjusting for individual covariates. The attenuated and non-significant association following adjustment indicates that if an association exists, it is weaker than has been suggested by some prior studies. The studies that reported significant associations between HSV-2 and schizophrenia also examined and controlled for a number of potential confounders, including gestational age (Mortensen et al., 2010), which may be important given that maternal serum IgG levels decrease throughout pregnancy (Ailus, 1994), and HSV-2 IgG antibodies in particular have been observed to decline (Arvaja et al., 1999). The gestational week of the blood draw, however, was not associated with HSV-2 seropositivity in our sample. The assay methods from these three studies were similar and thus are not likely to explain observed differences.

Given the prior association between schizophrenia and the general class of maternal STIs that were clinically documented during pregnancy (Babulas et al., 2006), it is also possible that an association with schizophrenia is due to an effect of other infections or of maternal immune activation during pregnancy (Brown and Patterson, 2011). Consistent with an immune activation hypothesis, we previously observed an increased risk of schizophrenia associated with higher prenatal maternal levels of C-reactive protein in this cohort (Canetta et al., 2014). If other infections or general immune activation are responsible for previously observed associations, differences between studies focusing on HSV-2 antibodies may stem from varying correlations across populations in the comorbidity rates with relevant infections, in particular, other STIs (Alberts et al., 2013). Other population differences that may have contributed to the variation in findings across studies include differences in the rates of re-activation of prior HSV-2 infection (Frenkel et al., 1993), re-exposure to HSV-2 infection (Buka et al., 2008) during pregnancy, or in the prevalence of genotypes that might modify the risk associated with HSV-2 exposure (Carter, 2009).

Studies have reported associations between *C. trachomatis* IgG seropositivity and the risk of pregnancy complications including infertility (Coppus et al., 2011; Salmani et al., 2011), ectopic pregnancy (Li et al., 2014), spontaneous abortion (Salmani et al., 2011; Wilkowska-Trojniel et al., 2009; Witkin and Ledger, 1992) and stillbirth (Gencay et al., 2000), although these associations have not been entirely consistent (Paukku et al., 1999; Rae et al., 1994). We did not find even suggestive evidence for an association between *C. trachomatis* seropositivity and schizophrenia diagnosis in the offspring. This is in concordance with the one other study (Buka et al., 2001) that previously examined this relationship. The potential role of incident *C. trachomatis* infection during pregnancy, however, remains unknown given that seropositive women may have a history of past, but not current or recent infection.

We note the following limitations. Although the sample size for *C. trachomatis* was modest relative to that for HSV-2, it included several times as many cases as the prior study just cited (Buka et al., 2001). The fact that the samples in this study were drawn relatively early in pregnancy does not allow us to address the potential effects of any new infections with HSV-2 or *C. trachomatis* acquired during later pregnancy, and no samples are available from late pregnancy or the neonatal period, including filter paper blood spots. However, the number of new infections is likely to be small for both HSV-2 and *C. trachomatis*, as discussed above. However, it may be informative for future studies to distinguish between past and current infections. Information on other infections is not yet available, though is a focus of future work in this birth cohort.

The strengths of this investigation were considerable. The study was based on a national birth cohort and the sample sizes were the largest to date among studies of maternal HSV-2 and *C. trachomatis* and schizophrenia. Antibodies were measured in prospectively collected archived maternal serum samples. Selection bias was limited because the study was based on registries and a serum repository that cover essentially the entire population. Moreover, because health care is available at no or minimal cost to all residents, ascertainment of cases is relatively complete and there is a far lower risk of bias compared to clinical samples or those obtained from cases drawn from selected regions within a country. Finally, facilitated by the registry linkages, we had access to data on a wealth of covariates in order to allow control for potential confounders.

In conclusion, we did not find definitive evidence for associations of early to mid-gestational levels of maternal HSV-2 or *C. trachomatis* IgG antibodies with schizophrenia among offspring. Given emerging evidence linking other prenatal maternal infections with risk of schizophrenia, and the possibilities for prevention of psychiatric morbidity that may exist therein, research to determine the specific infectious agents or immune processes involved remains critical. We suggest that future studies should address other infections during pregnancy, including incident STIs, in relation to schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Characteristics of cases with schizophrenia and controls

Characteristic	Cases	Controls	p-value
	n=963	n=963	
Maternal age, mean (SD)	28.3 (5.5)	28.0 (5.1)	0.20
Paternal age, mean (SD)	31.0 (6.1)	30.4 (5.7)	0.03
Male, %	58.1%	58.1%	1.00
>=1 previous birth (versus 0), %	62.1%	62.0%	0.96
Maternal education, % *			
Secondary school only	25.5%	22.5%	0.27
Vocational degree/secondary school graduate	57.5%	57.7%	
College degree/bachelor university degree	11.8%	13.9%	
Master degree/licenciate degree/PhD	5.2%	5.9%	
Paternal education, % *			
Secondary school only	31.1%	26.3%	0.03
Vocational degree/secondary school graduate	51.1%	57.3%	
College degree/bachelor university degree	7.8%	8.1%	
Master degree/licenciate degree/PhD	10.0%	8.3%	
Maternal psychiatric disorders			
Schizophrenia/non-affective psychosis	10.2%	1.8%	<0.0001
Affective disorders	20.9%	8.4%	<0.0001
Any psychiatric disorder	32.2%	13.8%	<0.0001
Parental psychiatric disorders			
Schizophrenia/non-affective psychosis	16.4%	3.1%	<0.0001
Affective disorders	30.5%	13.3%	<0.0001
Any psychiatric disorder	49.6%	23.3%	<0.0001
Gestational age <37 weeks (versus >=37 weeks) *	7.3%	5.0%	0.08
Gestational week of blood draw *			
Observed completed with estimated, mean (SD)	11.0 (3.9)	10.8 (3.9)	0.38
Twin birth (versus singleton) *	1.9%	4.4%	0.002
Municipality of birth			
Rural	24.5%	30.0%	0.005
Semi-urban	12.1%	13.7%	
Urban	63.5%	56.3%	
Province of birth			
Eastern Finland	11.9%	15.1%	<0.0001
Northern Finland	12.6%	14.1%	
Southern Finland	48.6%	35.9%	
Western Finland	26.9%	34.9%	

* Missing observations: maternal education, n=6; paternal education, n=35; gestational age, n=565; gestational week of blood draw, n=271; plurality, n=6.

Table 2

Associations between covariates and maternal seropositivity to HSV-2 and Chlamydia trachomatis IgG among control subjects

	HSV-2			C. trachomatis		
	Positive	Negative	p-value	Positive	Negative	p-value
Characteristic	**n=121**	**n=819**		**n=32**	**n=159**	
Maternal age, mean (SD)	29.2 (4.7)	27.8 (5.1)	0.01	27.6 (4.7)	28.7 (4.7)	0.20
Paternal age, mean (SD)	31.8 (5.7)	30.2 (5.6)	0.003	30.0 (5.4)	30.7 (5.2)	0.51
Male, %	67.8%	56.3%	0.02	64.5%	59.4%	0.70
>=1 previous birth (versus 0), %	63.6%	61.4%	0.64	46.9%	61.6%	0.12
Maternal education, %			0.95			0.53
Secondary school only	23.1%	22.2%		15.6%	17.0%	
Vocational degree/secondary school graduate	57.9%	58.0%		75.0%	62.3%	
College degree/bachelor university degree	14.1%	13.6%		6.3%	15.7%	
Master degree/licenciate degree/PhD	5.0%	6.3%		3.1%	5.0%	
Paternal education, %			0.37			0.15
Secondary school only	27.3%	25.8%		38.7%	20.1%	
Vocational degree/secondary school graduate	60.3%	57.0%		51.6%	60.4%	
College degree/bachelor university degree	8.3%	8.3%		3.2%	5.0%	
Master degree/licenciate degree/PhD	4.1%	8.9%		6.5%	14.5%	
Maternal psychiatric disorders						
Schizophrenia/non-affective psychosis	3.3%	1.6%	0.26	0.0%	1.9%	1
Affective disorders	11.6%	7.8%	0.16	3.1%	5.0%	1
Any psychiatric disorder	18.2%	13.2%	0.14	6.3%	9.4%	0.74
Parental psychiatric disorders						
Schizophrenia/non-affective psychosis	5.8%	2.7%	0.07	3.1%	3.1%	1
Affective disorders	17.4%	12.5%	0.14	9.4%	9.4%	1
Any psychiatric disorder	27.3%	22.7%	0.27	12.5%	17.0%	0.79
Gestational age <37 weeks (versus >=37 weeks)	3.8%	5.2%	0.79	0.0%	5.9%	1
Gestational week of blood draw	10.6 (3.6)	10.9 (4.0)	0.56	9.6 (2.6)	10.3 (3.8)	0.33
Twin birth (versus singleton)	5.0%	4.3%	0.74	3.1%	3.1%	1.0
Municipality of birth			0.14			0.02
Rural	23.1%	30.9%		12.5%	34.0%	
Semi-urban	12.4%	13.9%		12.5%	17.6%	
Urban	64.5%	55.2%		75.0%	48.4%	
Province of birth			0.04			0.28
Eastern Finland	14.9%	15.0%		6.3%	18.2%	
Northern Finland	9.1%	14.8%		9.4%	14.5%	
Southern Finland	47.1%	34.7%		40.6%	33.3%	
Western Finland	28.9%	35.5%		43.8%	34.0%	

Table 3

Odds ratios and 95% confidence intervals for the association of schizophrenia with maternal HSV-2 IgG seropositivity and levels among cases and matched controls with non-equivocal assay results

	Schizophrenia	Controls	Model 1[a]		Model 2[b]	
	N (%)	N (%)	OR	95% CI	OR	95% CI
HSV-2 IgG treated as a dichotomous variable [c]						
Seropositive	158 (16.4)	121 (12.6)	1.33	1.03, 1.72	1.20	0.91, 1.60
Seronegative	792 (82.2)	819 (85.1)	1.00	Ref	1.00	Ref
HSV-2 IgG treated as a continuous variable						
Log transformed HSV-2 IgG level	--	--	1.21	0.99, 1.47	1.12	0.90, 1.39

[a] Unadjusted; based on 950 cases and 940 controls with non-equivocal HSV-2 IgG measurements (927 complete case-control pairs).

[b] Adjusted for paternal age, province of birth, and parental schizophrenia diagnosis; based on 929 cases and 934 controls with non-equivocal HSV-2 IgG measurements and complete covariate data (900 complete case-control pairs).

[c] Percentages do not sum to 100 due to 13 (1.4%) cases and 23 (2.4%) controls with equivocal values for HSV-2 IgG. These observations were excluded from models due to non-interpretability.