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ORIGINAL PAPER

Maternal Infection Requiring Hospitalization During Pregnancy and Autism Spectrum Disorders

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Abstract Exposure to prenatal infection has been suggested to cause deficiencies in fetal neurodevelopment. In this study we included all children born in Denmark from 1980, through 2005. Diagnoses of autism spectrum disorders (ASDs) and maternal infection were obtained through nationwide registers. Data was analyzed using Cox proportional hazards regression. No association was found between any maternal infection and diagnosis of ASDs in the child when looking at the total period of pregnancy: adjusted hazard ratio = 1.14 (CI: 0.96–1.34). However, admission to hospital due to maternal viral infection in the first trimester and maternal bacterial infection in the second trimester were found to be associated with diagnosis of ASDs in the offspring, adjusted hazard ratio = 2.98 (CI: 1.29–7.15) and adjusted hazard ratio = 1.42 (CI: 1.08–1.87), respectively. Our results support prior hypotheses concerning early prenatal viral infection increasing the risk of ASDs.

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Introduction

Autism spectrum disorders (ASDs) are child neurodevelopmental disorders characterized by impairments in social interactions, communication, and a stereotyped, repetitive repertoire of interests and activities (World Health Organization 1993).

Increases in reported prevalence of ASDs in recent years have fuelled concerns over possible environmental causes (Blaxill 2004). Case reports and comparative studies have suggested maternal prenatal viral infections, such as rubella (Libbey et al. 2005; Deykin and MacMahon 1979; Chess 1977) and cytomegalovirus (Libbey et al. 2005; Sweeten et al. 2004; Yamashita et al. 2003) to be associated with the development of ASDs in the offspring. Libbey et al. (2005) proposed that prenatal infection might lead to ASDs in genetically susceptible individuals; an acute infection in the mother during pregnancy could lead to transient high levels of cytokines affecting the developing brain of the fetus, or acute infection could initiate an autoimmune process resulting in a maternal inflammatory response with high cytokine levels throughout the remainder of the pregnancy. A persistent viral infection could also lead to chronically elevated cytokine levels resulting in fetal brain damage. Ponzio et al. (2007) used a prenatal mouse model to study the ability of certain cytokines to cross placenta; hypothesizing that increased levels of maternal IL-2 during pregnancy induces, in the offspring, a long-lasting increased vulnerability to neurobehavioral abnormalities. Smith et al. identified IL-6 as a key mediator of the effects

of maternal immune activation on fetal brain development (Smith et al. 2007).

The literature lacks reports from epidemiological studies investigating the association between maternal infection during pregnancy and the development of ASDs in the offspring (Patterson 2009). This study investigates the association between a broad range of maternal infections requiring hospitalization during pregnancy, and the diagnosis of ASDs in the offspring.

Methods

Study Population

We used data from the Danish Medical Birth Register (Knudsen and Olsen 1998) to identify all children born in Denmark from January 1, 1980, through December 31, 2005 (1,612,342 children). The register is linked to the Danish Register of Causes of Death every year. All citizens in Denmark are assigned a personal identification number (CPR number) at birth, which is a unique 10-digit number used for all official personal registrations in Denmark since 1968 (Pedersen et al. 2006). The CPR number was used as a key to individual information in all national registers ensuring accurate linkage of information between registers.

Diagnostic System

The International Statistical Classification of Diseases, 8th version (ICD-8; World Health Organization 1965) was used as a diagnostic instrument by medical doctors in Denmark from 1969 through 1993. In 1994, ICD-8 was replaced by the 10th version (ICD-10; World Health Organization 1993) which is still used today. ICD-10 is comparable to DSM-IV criteria.

Outcome Data

Cohort data on ASDs diagnoses were found in the Danish Psychiatric Central Register (Munk-Jorgensen and Mortensen 1997). The psychiatric register includes information on all inpatient admissions to psychiatric hospitals and psychiatric wards in general hospitals in Denmark since 1969, and all outpatient contact since 1995. Registered diagnoses are made by psychiatrists. Children, who are suspected to have ASDs, are referred by general practitioners or school psychologists to a child psychiatric clinic where they are diagnosed and treated by a psychiatrist. Cohort members were classified with ASDs if they had been admitted as an inpatient or been in outpatient care with a diagnosis in the autism spectrum: childhood autism, atypical autism, Asperger's syndrome, and other/unspecified pervasive developmental disorders (ICD-10 codes: F84.0, F84.1, F84.5, F84.8, F84.9 and ICD-8 codes: 299.00, 299.01, 299.02, 299.03).

Exposure Data

Exposure data were obtained from the Danish National Hospital Register (DNHR; Andersen et al. 1999). The hospital register was initiated in 1977, and includes detailed information on all hospital admissions in the entire country. We only included the primary diagnosis of mothers registered as admitted patients. We included infectious diagnoses given between date of last menstruation and date of birth, or within the relevant trimester. Gestational age was determined by the midwife/doctor using information from ultrasound and/or the date of last menstrual period. We calculated the date of last menstruation by subtracting the gestational age from the date of birth. First trimester was defined as the period from 'date of last menstruation' through 'date of last menstruation plus 92 days', second trimester was the period from 'date of last menstruation +93 days' through 'date of last menstruation +184 days', third trimester was the period from 'date of last menstruation +185 days' until 'birth'.

We analyzed the infection data in the following three broad categories (Table 1): *Any infection;* defined as all infections registered for the mother during pregnancy, *Microorganism-specific Infection Categories;* including viral infections, and bacterial infections, and *Organ-specific Infection Categories*; including six subgroups. While the diagnoses in the microorganism-specific subgroups overlap somewhat with the diagnoses in the organ-specific subgroups, the diagnoses within each subgroup of a category are mutually exclusive. However, a woman can be included in more than one subgroup if she had different infectious admissions. Infection categories were chosen according to clinical relevance and after systematically assessing all potential infection diagnostic codes. In order to obtain reliable risk estimates, analyses were made only for infectious diseases for which at least five ASDs cases were exposed. Infection groups that were excluded due to low number of exposed outcome are listed in Table 1 (footnote).

Analytic Approach

The hazard ratio (HR) of ASDs was estimated by Cox proportional hazard models, with age of the child as the underlying time scale. Survival analyses methods adjusted for the difference in follow-up time; follow-up time ended at the first date of reported ASDs diagnosis, death, or on December 31, 2008. The proportional hazard assumption was evaluated for all variables by comparing estimated

Table 1 ICD-8 and ICD-10 diagnostic codes of infectious diseases categories

	ICD-8	ICD-10
Any infection	000–136, 780.21, 788.89 + all below	A00–B99, G00–G09, R50.9, R56.0 + all below
Microorganism-specific infection categories		
Virus infection	008.8–008.9, 040–079, 381.00, 470–474, 480	A08, A80–A99, B00–B34, B97, G02.0, G05.1, H67.1, J10–J12, J17.1, J20.3–J20.7, J21.0, M01.4–M01.5
Bacterial infection	000–005, 008.0–008.3, 010–039, 079.84, 090–104, 320–324, 381.01, 390–391, 464.03, 481–482, 501, 508.00–508.03, 510, 513, 540–542, 590, 595, 599.00, 599.06, 612–614, 616.0, 620, 622, 630, 635, 680–686, 710	A00–A05, A15–A59, A65–A79, B95–B96, G00, G01, G04.2, G05.0, G06–G09, H66, H67.0, I00–I01, J13–J15, J17.0, J20.0–J20.2, J36, J39.0–J39.1, J85–J86, K35–K37, L00–L08, M00, M01.0–M01.3, N10–N12, N30, N34.0, N39.0, N70–N77, O23
Organ-specific infection categories		
Respiratory infection	032–034, 460–474, 480–486 491.01, 501, 503, 506, 508.00–508.05, 510–511, 513	A36–A38, J00–J22, J32, J36–J37, J39.0–J39.1, J85–J86
Infectious enteritis	001–009	A01–A09
Skin infection	680–686	L00–L08
Urinary tract infection	590, 595, 599.00, 599.06, 635	N10–N12, N30, N34.0, N39.0, O23.0–O23.4
Genital infection incl. STDs[a]	054.02, 079.84, 090–099, 131, 612–614, 616.0, 620, 622, 630	A50–A64, N70–N77, O23.5–O23.9
Appendicitis	540–542	K35–K37

The infections shown are only those where at least 5 cases were exposed. Specific categories with fewer than 5 exposed cases included influenza, mycoses infection, infection in the central nervous system, meningitis, septicemia, purulent arthritis, eye infection, ear infection, lyme disease, infection with toxoplasmosis, rubella, parvovirus, infections with human herpes virus combined as well as specifically cytomegalovirus, varicella, and herpes simplex virus

[a] Sexually transmitted diseases (STDs) include syphilis, Gonorrhea, Chlamydia, trichomoniasis, condyloma and genital herpes

log − log survivor curves over the different categories of variables investigated. Adjusted hazard ratios (aHR) were adjusted for potential confounders: sex of the child, maternal age at birth of child, paternal age at birth of child, parity, and a dichotomous variable indicating whether or not either parent had a history of psychiatric diagnosis prior to the birth of the child (ICD-8: 310–315, ICD-10: F7). Birth weight and gestational age are potential intermediary variables; therefore, they were not included in the analysis as potential confounders. However, including birth weight and gestational age in the analyses did not change the results. All covariates were included as categorical variables (categories listed in Table 2). In order to adjust for changes in HR over calendar time, all analyses were made in strata specific for year of birth in specific groups (Table 2). Data on parental age, gestational age, birth weight, sex and parity was retrieved from the birth registry (Knudsen and Olsen 1998), and data on parent's psychiatric history were retrieved from the psychiatric registry (Munk-Jorgensen and Mortensen 1997). Only 4.4 percent of observations were excluded from analyses due to missing variables (Table 2). To account for the lack of independence of children within the same family, we used a robust (Huber–White) variance estimator which allowed for clustering of outcomes within a family. Statistical analyses were performed using STATA statistical software, version 10.

Primary Analyses

The main association investigated was the relationship between the mother's hospitalization due to a particular infection at any time during the whole pregnancy, and the diagnosis of ASDs in the corresponding offspring. Also, we analyzed data according to which trimester the mother was admitted to hospital, due to a particular infection.

Secondary Analyses

We investigated whether the rate of ASDs diagnosis in the offspring increased with number of maternal admissions to hospital during the pregnancy due to any infection. If less than 7 days passed between an individual's registered discharge from hospital and a subsequent admission to hospital, the two hospitalizations were considered as one infection incident.

We investigated whether the effect between any maternal infection during pregnancy and diagnosis of ASDs was modified by: (a) gestational age (<37 weeks and ≥37 weeks), (b) birth weight (<2,500 and ≥2,500 grams), (c) year of birth (1980–1994 and 1995–2005), or (d) sex of the child. Furthermore, we investigated the relationship between any maternal infection during pregnancy and childhood autism (children displaying symptoms

Table 2 Characteristics of the study population

Characteristic	Mother hospitalized due to infection (%; $n = 21,266$)	Mother not hospitalized due to infection (%; $n = 1,591,076$)
ASDs	156 (0.7)	9,977 (0.6)
Gender		
Male	10,812 (50.8)	816,699 (51.3)
Female	10.454 (49.1)	774,377 (48.7)
Mothers age, *y*		
≤25	7,661 (36.0)	343,720 (21.6)
26–34	11,831 (55.6)	1,064,460 (66.9)
≥35	1,774 (8.3)	182,896 (11.5)
Fathers age, *y*		
<25	3,992 (18.8)	161,888 (10.2)
26–30	6,689 (31.5)	485,960 (30.5)
31–35	5,803 (27.3)	528,427 (33.2)
≥35	4,427 (20.8)	399,292 (25.1)
Missing	355 (1.7)	15,509 (1.0)
Gestational age, weeks		
<28	71 (0.3)	3,851 (0.3)
28–32	171 (0.8)	10,299 (0.7)
32–37	1,435 (6.8)	76,764 (4.9)
>37	19,589 (92.1)	1,471,340 (94.2)
Missing		28.822 missing values
Birth weight, gram		
<2,500	1,491 (7.0)	82,406 (5.2)
2,500–2,999	3,276 (15.4)	194,973 (12.3)
3,000–3,500	7,286 (34.3)	513,586 (32.3)
>3,500	9,139 (43.0)	791,344 (49.7)
Missing	74 (0.4)	8,767 (0.6)
Parity		
1st child	10,899 (51.3)	709,900 (44.6)
≥2 children	10,101 (47.5)	863,400 (54.3)
Missing	266 (1.3)	17,776 (1.1)
Parent with psychiatric disorder		
No	20,254 (95.2)	1,546,052 (97.2)
Yes	1,012 (4.8)	45,024 (2.8)
Year of birth		
1980–1984	3,182 (15.0)	262,477 (16.5)
1985–1989	4,098 (19.3)	281,378 (17.7)
1990–1994	4,515 (21.2)	328,029 (20.6)
1995–1999	4,240 (19.9)	333,498 (21.0)
2000–2005	5,231 (24.6)	385,694 (24.2)

of autism before 3 years of age are diagnosed with childhood autism, hence childhood autism is a more homogeneous group compared to the whole spectrum). Due to low number of exposed outcome, secondary analyses were not performed for infectious subgroups or separate trimesters. However, we did study the association between viral infection in the first trimester and bacterial infection in the second trimester, and ASDs including only children born 1994–2005.

Validation

We investigated the accuracy of information in the DNHR by doing a small validation; we evaluated random medical

records for 20 pregnant women registered in the DNHR as having a viral infection, and 20 pregnant women registered as having a bacterial infection. All 40 women were diagnosed using ICD-10 diagnostic criteria.

The study was approved by the Danish Data Protection Agency and the Danish National Board of Health.

Results

A total of 10,133 children were diagnosed with ASDs. Participant characteristics by exposure status show that children with mothers hospitalized due to infection during pregnancy were more likely to have younger parents, have a low birth weight, be a first born child, and have parents with a psychiatric diagnosis (Table 2). The mean follow-up time was 15.1 years, and 13,899 children died during follow-up. The mean age of ASDs diagnosis was 9.3 years.

Primary Analyses

When looking at all maternal infections combined during the total length of the pregnancy, no association was observed with the diagnosis of ASDs in the offspring: aHR = 1.14 (CI: 0.96–1.34). Also, maternal hospitalization due to specific infection categories during the total pregnancy period was not associated with ASDs in the offspring; the aHR ranged from aHR = 0.72 (CI: 0.39–1.33) for maternal hospitalization due to infectious enteritis, to aHR = 1.55 (CI: 0.88–2.74) for maternal skin infection during pregnancy (Table 3). When stratifying by trimester, the association between maternal infection and ASDs in the offspring remained insignificant in most cases (Table 4), however, with few exceptions. Viral infection in the mother during first trimester was associated with a diagnosis of ASDs in the child: aHR = 2.98 (CI:1.24–7.15), and admission to hospital due to any infection during second trimester was associated with the development of ASDs in the offspring: aHR = 1.30 (CI: 1.01–1.67), an association driven by bacterial infection: aHR = 1.42 (CI: 1.08–1.87).

Secondary Analyses

No association was found between number of admissions due to infection during pregnancy and diagnosis of ASDs in the offspring: one admission: aHR = 1.03 (CI: 0.97–1.09), two admissions: aHR = 1.08 (CI: 0.99–1.19) and three admissions: aHR = 1.00 (CI: 0.87–1.14), $p = 0.186$ from a test of trend.

Birth weight, gestational age, year of birth, and sex of the child did not modify the association between maternal admission to hospital during pregnancy due to any infection, and diagnosis of ASDs in the child. (a) Gestational age: <37 weeks: aHR = 1.55 (CI: 0.98–2.44), ≥37 weeks: aHR = 1.09 (CI: 0.91–1.30), *p*-value for interaction = 0.166, (b) birth weight: <2,500 gram: aHR = 1.39 (CI: 0.85–2.29), ≥2,500 gram: aHR = 1.11 (CI: 0.93–1.32), *p*-value for interaction = 0.442, (c) year of birth: 1980–1993: aHR = 1.10 (CI: 0.88–1.38), 1994–2005: aHR = 1.18 (CI: 0.92–1.51), *p*-value for interaction = 0.641, (d) sex of the child: male: aHR = 1.15 (CI: 0.96–1.38), female: aHR = 1.08 (CI: 0.74–1.58), *p*-value for interaction = 0.788. Any infection during pregnancy was not associated with childhood autism; aHR = 1.07 (CI: 0.73–1.56). Viral infection during first trimester was found associated with a diagnosis of ASDs in children born 1994–2005: aHR = 3.14 (CI: 1.02–9.67), however,

Table 3 The hazard ratio (HR) of autism spectrum disorders after maternal admission to hospital due to infection during pregnancy

	Number of exposed ASDs/non-ASDs	Crude HR (95%CI)	aHR[a] (95%CI)
Any infection	156/21,110	1.16 (0.99–1.36)	1.14 (0.96–1.34)
Microorganism-specific infection categories			
Viral infection	9/1,550	0.96 (0.50–1.85)	0.85 (0.42–1.70)
Bacterial infection	122/15,810	1.21 (1.01–1.45)	1.21 (1.00–1.45)
Organ-specific infection categories			
Respiratory infection	12/1,883	1.07 (0.61–1.88)	1.00 (0.55–1.80)
Infectious enteritis	11/2,262	0.75 (0.40–1.39)	0.72 (0.39–1.33)
Skin infection	12/1,329	1.51 (0.86–2.66)	1.55 (0.88–2.74)
Urinary tract infection	68/8,734	1.30 (1.02–1.65)	1.17 (0.91–1.51)
Genital infection incl. STDs	29/4,157	0.99 (0.69–1.42)	1.07 (0.74–1.55)
Appendicitis	15/1,833	1.22 (0.74–2.03)	1.31 (0.77–2.21)

[a] Hazard ratios were adjusted for maternal age, paternal age, parity, sex of the child, and parents' psychiatric condition. Data was analyzed in strata by year of birth. Pregnant women without admission to hospital due to the particular infection were chosen as the reference category

Table 4 The adjusted hazard ratio (aHR) of autism spectrum disorders after maternal admission to hospital due to infection during pregnancy, stratified by trimester

	1. Trimester aHR[a] (95%CI)	2. Trimester aHR[a] (95%CI)	3. Trimester aHR[a] (95%CI)
Any infection	1.28 (0.91–1.81)	1.30 (1.01–1.67)	0.90 (0.69–1.17)
Microorganism-specific infection categories			
Viral infection	2.98 (1.24–7.15)	NE	NE
Bacterial infection	1.07 (0.69–1.66)	1.42 (1.08–1.87)	1.04 (0.78–1.38)
Organ-specific infection categories			
Respiratory infection	1.97 (0.82–4.74)	NE	NE
Infectious enteritis	NE	1.13 (0.47–2.72)	NE
Skin infection	NE	2.13 (0.89–5.11)	NE
Urinary tract infection	1.21 (0.58–2.55)	1.12 (0.62–2.01)	1.10 (0.78–1.54)
Genital infection incl. STDs	0.79 (0.32–1.89)	1.43 (0.86–2.37)	0.70 (0.35–1.41)
Appendicit	NE	1.32 (0.63–2.77)	NE

NE not estimated

[a] Hazard ratios were adjusted for maternal age, paternal age, parity, sex of the child, and parents' psychiatric condition. Data was analyzed in strata by year of birth. Pregnant women without admission to hospital due to the particular infection were chosen as the reference category

bacterial infection during second trimester lost its statistical significance when only including children born 1994–2005: aHR = 1.12 (CI: 0.71–1.79).

Validation

Medical records from 40 randomly selected women registered with infectious disease in the DNHR were reviewed. It was determined that for 95% of these women, the same diagnosis was reported in the medical record as in the DNHR.

Discussion

Our findings do not suggest an overall association between any maternal infection during pregnancy, and diagnosis of ASDs in the child. However, our results support hypotheses concerning viral infection during first trimester and the development of ASDs in the offspring. In addition we observed an association between bacterial infection during second trimester, and the diagnosis of ASDs in the child.

Limitations

We had no information on specific symptoms of the infection, such as fever, and we were not able to consider the effects of specific anti-infective medical treatments that might have been administered during hospitalization. We had limited information on co-occurring infections since the data were analyzed by the primary diagnosis, and the quality of the register data on secondary diagnosis is uncertain. We only included infections requiring admission to hospital and it is reasonable to assume that the infectious diseases included were the most severe ones; hence we were unable to investigate the effect of subclinical infection, as well as the many infections treated by a general practitioner. Collier et al. reported the prevalence of self-reported infection among pregnant women and 63.6% of women reported at least one infection during pregnancy (Collier et al. 2009). Only 1.3% of the women in our study population were admitted to hospital due to infection. We found no studies reporting the prevalence of hospital admission due to infection during pregnancy. We potentially missed some diagnoses of ASDs made before 1995; children only seen in outpatient clinic from 1980 to 1994 and with no contact to a psychiatric clinic after 1994 are not registered in the psychiatric register, however, this misclassification is likely non-differentiated with respect to maternal infection since there is little difference in results for children born before and after 1995.

It is important to emphasize that this study is an exploratory study; hence we did not adjust for multiple testing. We made a total of 33 comparisons and the significant associations observed could therefore be chance findings (type 1 error).

Quality of Data

The quality of childhood autism diagnoses found in the psychiatric register have been validated; after evaluating 499 medical records of children registered with childhood autism, 94% met the criteria for a correct diagnosis (Lauritsen et al. 2010). The completeness of ASDs diagnosis in the register is assumed to be good; the prevalence of ASDs for 9-year old children is reported to be 6.2 per thousand

(Parner et al. 2008), an estimate similar to the American prevalence of 9 per thousand for 8-year old children found in surveillance studies (Autism and Developmental Disabilities Monitoring Network 2009).

The quality of ICD-8 diagnoses reported to the DNHR in 1990 has been evaluated; 27 infectious diagnoses from medical wards nationwide were validated and 70.4% of the main diagnoses were correctly entered in the registry, according to the person's medical record. It is assumed that the introduction of the ICD-10 diagnostic system in 1994 created more clear-cut rules for choice of primary diagnosis, resulting in even better validity of the registry (Mosbech et al. 1995). The authors found a 95 percent concordance of ICD-10 diagnoses between the hospital register and the medical record.

Interpretation of Results

A statistically significant association was found between maternal viral infection during the first trimester and ASDs in the child. A total of 283 children were exposed to viral infection in the first trimester, this group included a broad variety of different viral infections, the most common ones being influenza (25%), viral gastroenteritis (20%), and unspecified viral infection (12%). The observed association between viral infection in the first trimester and ASDs is possibly driven by influenza virus; our data included only six children, diagnosed with ASDs, born by mothers admitted to hospital due to a viral infection during the first trimester, and three out of those six mothers were admitted due to influenza virus. Shi et al. (2003) concluded from an animal study that the offspring of influenza-infected mice display abnormal behavioral responses; i.e. deficient exploratory behavior in open-field and novel-object tests, and deficient social interaction. These alterations in behavior likely reflect hyperanxiety in novel and stressful situations, which is associated with autism. Furthermore, Shi et al. suggested that the alterations in behavior were attributable to the maternal immune activation and not the influenza virus itself, because they observed the same effect on the murine offspring after merely evoking the maternal inflammatory response using synthetic double-stranded RNA poly(I:C), i.e. without directly exposing the fetus to the virus (Shi et al. 2003). In further support of hypotheses suggesting that prenatal influenza infection affects the fetal brain development, Brown et al. found that maternal infection with influenza during first trimester increases the risk of schizophrenia (Brown et al. 2004a).

Results from an ecological study contradict this proposed association between prenatal influenza infection and ASDs; Dassa et al. found no increased risk of ASDs among individuals who were at increased risk of prenatal exposure to influenza virus, however, the authors point out that lack of statistical power can possible explain the negative findings. Furthermore, many previous studies have looked at seasonal variation in the birth of children with ASDs, using this as a proxy measure for risk factors with a seasonal variation, such as influenza infection. Earlier studies found an increased risk of developing autism among children born in March (Barak et al. 1995; Gillberg 1990) while more recent studies have reported no seasonal variation (Landau et al. 1999; Atladottir et al. 2007).

Several case reports have associated ASDs with various congenital viral infections, such as rubella (Libbey et al. 2005; Deykin and MacMahon 1979; Chess 1977) or infection with cytomegalovirus (Libbey et al. 2005; Yamashita et al. 2003; Sweeten et al. 2004). The present study was not able to validate these specific associations because of a low exposed case count; during our study period only 7 mothers were admitted due to cytomegalovirus and 19 mothers were admitted due to rubella; none of their children were diagnosed with ASDs. The low incidence of rubella mirrors the success of vaccination for rubella in Denmark; seronegative women of childbearing age have been vaccinated since 1980. Infection with cytomegalovirus most often results in mild or even subclinical symptoms, which do not require hospitalization.

We observed a relationship between bacterial infection during the second trimester, and diagnosis of ASDs in the child. Studies on exposure to maternal bacterial infection during pregnancy, and the development of ASDs in offspring are lacking and the present finding needs to be replicated in other study populations since this is possibly a chance finding. However, studies have looked at the association between bacterial infection and schizophrenia. Sorensen et al. (2009) observed an increased risk of schizophrenia after prenatal exposure to bacterial infection in the first trimester of pregnancy, an association primarily driven by respiratory infection and gonococcal infection. In our study population, a total of 5,981 children were exposed to bacterial infection in the second trimester, the most common bacterial infections were urinary tract infection (51%) and genital infection incl. STDs (24%). Only 1% of the women were admitted due to a respiratory infection. The association observed could be a result of transplacental passage of maternally produced cytokines or antibodies in response to the infection. It has been suggested that maternal antibodies to polysialic acid capsulated *E. coli* K1 and meningococcus bacteria can cross the placenta and cross-react with molecules containing sialic acid epitopes which are present during the development of the nervous system. An example of such a molecule is the neural cell adhesion molecule which is important in a variety of neurological functions (Nahmias et al. 2006). Moreover, a study by Brown et al. found elevated second trimester levels of interleukin-8 in mothers of individuals

who developed schizophrenia (Brown et al. 2004b). Interleukin-8 enhances the growth-inhibitory activity of neutrophils to pathogens (Djeu et al. 1990).

Additional studies are needed on the association between infections in the mother during pregnancy, and diagnosis of ASDs in the child. In particular, we need to study the effect of specific infections, such as influenza.

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