Published in final edited form as:
Brain Behav Immun. 2015 February ; 44: 100–105. doi:10.1016/j.bbi.2014.09.001.

Maternal hospitalization with infection during pregnancy and risk of autism spectrum disorders

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Abstract

Animal models indicate that maternal infection during pregnancy can result in behavioral abnormalities and neuropathologies in offspring. We examined the association between maternal inpatient diagnosis with infection during pregnancy and risk of ASD in a Swedish nationwide register-based birth cohort born 1984–2007 with follow-up through 2011. In total, the sample consisted of 2,371,403 persons with 24,414 ASD cases. Infection during pregnancy was defined from ICD codes. In the sample, 903 mothers of ASD cases (3.7%) had an inpatient diagnosis of infection during pregnancy. Logistic regression models adjusted for a number of covariates yielded odds ratios indicating approximately a 30% increase in ASD risk associated with any inpatient diagnosis of infection. Timing of infection did not appear to influence risk in the total Swedish population, since elevated risk of ASD was associated with infection in all trimesters. In a subsample analysis, infections were associated with greater risk of ASD with intellectual disability than for ASD without intellectual disability. The present study adds to the growing body of evidence, encompassing both animal and human studies, that supports possible immune-mediated mechanisms underlying the etiology of ASD.

Keywords

autism; infection; cytokines; epidemiology

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Conflict of interest statement: All authors declare that there are no conflicts of interest.

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1. Introduction

Little is known about the etiology of autism spectrum disorders (ASD), but there is suggestive evidence for the role of environmental exposures during critical periods of early neurodevelopment (Newschaffer et al., 2007). Prenatal infection is a plausible risk factor for ASD, given that the teratogenic effect of prenatal infections such as rubella, cytomegalovirus or *Toxoplasma gondii* on the central nervous system is well established (Johnson, 1994). Numerous animal studies demonstrate that prenatal or early postnatal infections can result in both acute and persistent neurological and behavioral abnormalities in offspring resembling autistic traits or schizophrenia (Asp et al., 2009; Meyer et al., 2007; Patterson, 2011). However, the validity of such animal models for human ASD is uncertain.

The first studies suggesting an association of prenatal infection with ASD focused on viruses with affinity to the CNS based on the hypothesis of a direct neurotoxic effect. Epidemiological studies of small samples suggested that rubella (Chess et al., 1978; Deykin and MacMahon, 1979), measles, mumps, and influenza (Deykin and MacMahon, 1979) were associated with ASD. More recently, epidemiological studies have expanded infectious exposures to a wide range of viruses and also other pathogens including bacteria. The largest study of over 10,000 ASD cases drawn from Danish electronic health registers reported that maternal hospitalization for viral infection in the first trimester and any infection or bacterial infection in the second trimester were associated with increased ASD risk (Atladottir et al., 2010). However, epidemiological findings have not consistently found evidence of increased ASD risk with infection. For example, a California study of 407 ASD cases reported that hospitalization with infection was associated with increased risk (Zerbo et al., 2013), while a Swedish study of 1,216 ASD cases found no such evidence (Buchmayer et al., 2009),

In order to build the evidence base concerning prenatal infection and ASD risk, additional epidemiological studies are necessary. Moreover, as different subtypes of ASD may have different environmental components (Frazier et al., 2014), it is important to examine whether prenatal infection differentially influences ASD subtype risk (with or without intellectual disability). Here, we examined whether maternal hospitalization with infection during pregnancy, type of infection, and timing of infection influences risk of ASD in the largest study to-date. In a subsample of the Swedish population with information on ASD co-morbid with or without intellectual disability, we further examined the associations of prenatal infection with these different subtypes of ASD (Szatmari et al., 2007).

2. Methods

Overview

The Swedish population register system retains routinely collected health and sociodemographic data on the entire population of Sweden. The registers are cross-linked via each person's unique national registration number assigned to all Swedish residents at birth or upon migration to Sweden (Ludvigsson et al., 2009). The ascertainment of ASD in the total Swedish population is based on data from national registers primarily covering inpatient admissions. In the subsample study of ASD with or without co-morbid intellectual disability, we studied a subsample of the total Swedish population, the Stockholm Youth

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Cohort (SYC), for which ascertainment of ASD is based on national register data in addition to regional register data from outpatient, specialist, and treatment centers in Stockholm County. Consequently, while the total Swedish population sample is substantially larger, the SYC subsample has better ASD ascertainment and subtype information regarding comorbid intellectual disability.

2.1 Study sample and ASD case ascertainment

The sample in this study consisted of all individuals born in Sweden 1984–2007 and followed until December 31, 2011. All data are derived from linkages to national registers held by Statistics Sweden and the National Board of Health and Welfare. The National Patient Register contains data on all inpatient care in Sweden since 1973 and includes outpatient specialist care since 2001. ASD case status as of December 31, 2011, was defined as a recorded diagnosis of ICD-9 (299) or ICD-10 (F84) in the National Patient Register. A recent medical record review of autism in the National Patient Register following a CDC validation protocol confirmed the presence of DSM-IV autism in 83 of 88 persons (94.3%) (Ludvigsson et al., 2013). In total, 2,385,678 persons were in the 1984–2007 birth cohorts. After exclusion of observations with missing covariate data, the final sample consisted of 2,371,403 persons, with 24,414 identified ASD cases.

The Stockholm Youth Cohort is a register-based study with continuous enrollment comprising all individuals who were ever resident in Stockholm County as children (Idring et al., 2012b; Magnusson et al., 2012). All data are derived from linkages to national registers held by Statistics Sweden and the National Board of Health and Welfare, as well as regional registers held by the Stockholm County Council. In total, 501,271 persons were in the 1984–2007 birth cohorts and resident in Stockholm County for ≥4 years. ASD case status as of December 31, 2011 was ascertained according to a validated case-finding approach covering all pathways to ASD diagnosis and care in Stockholm County, described in detail elsewhere (Idring et al., 2012b). In brief, ASD case status was described following ICD-9 (299), ICD-10 (F84), and DSM-IV (299) classifications using 1) the National Patient Register; and regional registers including 2) the Habilitation Register; 3) the Clinical Database for Child and Adolescent Psychiatry; 4) the VAL database recording all inpatient and outpatient health services usage in Stockholm County since 1997. Determination of intellectual disability was based on ICD-9 (317–319), ICD-10 (F70–F79), and DSM-IV (317–319) classifications and supplemented with the Habilitation Register, which categorizes service recipients as having autism with or without intellectual disability. Expert review of medical records for 177 ASD cases indicated that 96% were consistent with a diagnosis of ASD (Idring et al., 2012b). After exclusion of observations with missing covariate data, the final sample consisted of 496,993 persons, with 9,585 identified ASD cases.

2.2 Maternal hospitalization with infection during pregnancy

Information on maternal hospital admissions with diagnoses of infection during the pregnancy period was obtained from ICD-8, -9, and -10 codes in the National Patient Register. The pregnancy period was calculated using the gestational age based on early second trimester ultrasound for 95% of women (Hogberg and Larsson, 1997) or first day of

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the last menstrual period for the remainder. Hospital admission records in the National Patient Register list one primary diagnosis and up to seven secondary diagnosis codes.

We considered a prenatal infection to have occurred if an ICD code for infection was found in the primary or secondary codes. The rationale for this was based on the consideration that regardless of whether a pregnant woman has a primary or secondary diagnosis of an infection, the fetus is still exposed to the infection. In addition, primary inpatient diagnoses for infection potentially reflect more severe infections and may not well-represent cases that resolve without treatment. By examining all recorded infections regardless of primary or secondary diagnosis, we were able to include some infections that would be more likely to not require hospitalization, potentially increasing the generalizability of results. This infectious exposure definition was used by Zerbo et al., although Atladottir et al. considered only primary diagnoses of infection. One potential concern with including both primary and secondary diagnoses of infection is that the primary diagnosis, whatever it may be, may confound an association observed between infection and ASD. Therefore, we adjusted for hospitalizations during pregnancy and performed two sensitivity analyses described below, examining robustness to confounding, as well as repeating analyses considering only primary inpatient diagnoses of infection during pregnancy.

ICD codes for infection are listed in Supplementary Table 1. We categorized infections according to type, timing, and site. Types of infection were: 1) *Any infection* – bacterial, viral, other and unknown regardless of site of infections 2) *Bacterial infection*; 3) *Viral infection*; and 4) *Other infection* (infection from primarily unknown agents as well as protozoa, helminth, or fungi). Timings of infection were assessed according to first, second, or third trimester of pregnancy. To be able to compare with previous work, sites of infection were categorized following (Atladottir et al., 2010; Zerbo et al., 2013), and included: CNS, gastrointestinal, genitourinary, respiratory, and skin infections.

Covariates—Covariates considered in analyses were identified *a priori* from the literature or prior work as being risk factors for ASD. Biological parents and dates of birth were identified from the Multi-generation Register. Following our previous work (Idring et al., 2014), maternal age and birth year were centered and entered into models as quadratic terms, and paternal age was entered as a continuous term. The Integrated Database for Labor Market Research provided information on individual-level disposable family income at time of birth, calculated after deductions of taxes and adjusted for family size. To account for inflation, family income was categorized into quintiles according to birth year. Maternal origin was obtained from the Register of Total Population and categorized as born in Sweden, in Europe outside Sweden, and outside Europe. History of inpatient and outpatient maternal psychiatric care before delivery (yes/no) was ascertained from the National Patient Register, the Stockholm Adult Psychiatric Care Register (containing adult psychiatric in- and out-patient care within Stockholm County since 1997), and the VAL database (Jorgensen et al., 2010). History of maternal inpatient care in the year before start of pregnancy (0, 1, 2, ≥3 episodes) was obtained from the National Patient Register. Adjustment for the number of maternal hospitalizations was performed in order to account for potential confounding due to co-morbid illnesses (e.g., immune-mediated or psychiatric conditions associated with both infection and autism) and/or healthcare-seeking behavior

(e.g., a tendency to seek healthcare for both mother and child). Sex of child and parity (1, 2, ≥3) were obtained from the Medical Birth Register.

2.3 Statistical analysis

The study examined associations of maternal hospitalization with infection during pregnancy and ASD, and whether type of infection and timing of infection mattered. We further examined in the SYC subsample the associations of infection and ASD with or without intellectual disability. Logistic regression models estimated odds ratios (ORs) and 95% confidence intervals (CI) adjusted for the aforementioned covariates, with cluster robust standard errors to account for non-independence within family clusters (multiple pregnancies per mother). Statistical analyses were performed using R version 3.0.2 (R Development Core Team, 2013).

We repeated analyses considering only hospitalizations with primary diagnoses of infection (i.e., maternal admission to hospital due to infection during pregnancy). In addition, we performed an additional sensitivity analysis to determine the robustness of any observed associations to unmeasured confounding using a standard formula-based approach (Lin et al., 1998). We assumed a binary confounder *U* existed such that *U* increased the risk of ASD, and that *U* was more prevalent in exposed mothers than in unexposed mothers. After specifying the strength of relationship of *U* with ASD, and the prevalences of *U* in the exposed and unexposed, we estimated odds ratios corrected for this unmeasured confounder *U* over a range of plausible parameters.

3. Results

In the total Swedish population, among the 24,414 ASD cases and 2,346,989 non-cases, 903 (3.7%) of ASD cases and 61,642 (2.6%) of non-cases had mothers had a hospitalization with an infection diagnosis during pregnancy. In the SYC subsample, 417 of 9,585 ASD cases (4.4%) and 16,352 of 487,408 non-cases (3.4%) had a hospitalization with an infection diagnosis during pregnancy. ASD cases were more likely to be male, first-born, have a lower household income, have mothers with a history of psychiatric care before delivery, and hospitalized the year prior to start of pregnancy (Table 1).

3.1 Inpatient diagnosis of maternal infection

Maternal inpatient diagnosis of infection during pregnancy was associated with higher odds of ASD (OR = 1.37, 95% CI: 1.28, 1.47) (Table 2). A higher risk of ASD was associated with maternal inpatient diagnosis with infection, regardless of whether the infection was bacterial, viral, or other/unknown. In analyses of site-specific infections, odds ratios across sites were generally above 1.0, however precision was limited and only respiratory infections were associated with ASD. In sensitivity analyses examining maternal hospitalizations with primary diagnoses of infection, ORs were slightly attenuated (e.g., for any infection, OR = 1.33, 95% CI: 1.20, 1.47) (Supplementary Table 2).

3.2 Timing of infection

In the total Swedish population, there were 86 ASD cases with maternal inpatient diagnosis of infection in the first trimester, 179 in the 2nd trimester, and 701 in the 3rd trimester (Supplementary Table 3). A higher risk of ASD associated with maternal inpatient diagnosis of infection was observed during the 1st trimester (OR = 1.24, 95% CI: 1.00, 1.55), 2nd trimester (OR = 1.38, 95% CI: 1.19, 1.61) and 3rd trimester (OR = 1.36, 95% CI: 1.26, 1.47) (Table 3). These results did not meaningfully differ when only primary inpatient diagnoses of infection were considered.

3.3 ASD with and without co-morbid intellectual disability (ID) in the SYC

Additional data in the SYC subsample enabled stratified analyses of ASD by the presence or absence of ID. Of the ASD cases, 7,181 (74.9%) did not have comorbid ID, while 2,404 (25.1%) had comorbid ID. Increased risk of ASD with inpatient diagnosis of infection during pregnancy was observed, regardless of presence or absence of ID. In general, larger odds ratios for ASD with comorbid ID were observed than for ASD without comorbid ID. For ASD without ID, the OR for inpatient diagnosis of infection was 1.19 (95% CI: 1.06, 1.34) (Table 4), while the estimate for ASD with ID was 1.50 (95% CI: 1.25, 1.81). Consistent associations of inpatient diagnosis of infection and ASD with ID were observed regardless of bacterial, viral, or other infection. In comparison, only bacterial infections were associated with ASD without comorbid ID.

3.4 Sensitivity of results to unobserved confounding

The results for any maternal inpatient infection, the most prevalent exposure, appeared to be robust to unmeasured confounding. For example, if there were an unmeasured confounder *U* that doubled the risk of ASD, and was 20% prevalent in mothers with an inpatient diagnosis of infection and only 5% prevalence in unexposed mothers, the confounder-corrected OR would be 1.20 (95% CI: 1.12, 1.29, Table 5) as opposed to the OR of 1.37 (95% CI: 1.28, 1.47) reported in Table 1. Further, at the respective prevalences of 20% and 5% in the exposed and unexposed, *U* would have to increase the risk of ASD by 3 times – after adjustment for all of the model covariates – in order to decrease estimates such that the 95% CI no longer included 1. These sensitivity analyses suggest that it is unlikely that such an unmeasured confounder or residual confounding could wholly explain our findings. Because of reduced sample size, findings reported for organism- or site-specific infection exposures would not demonstrate similar robustness to unmeasured confounding, although the likelihood of distinct confounders operating for these specific exposures is unlikely.

4. Discussion

Our study of maternal hospitalization with infection and ASD in a large Swedish cohort yielded four main findings. First, maternal inpatient diagnosis of any infection during pregnancy was associated with an increased risk of ASD in the child; these associations appeared somewhat robust to unmeasured confounding. Second, increased risk was observed for a broad spectrum of infectious agents, including bacterial, viral, and other infections. Third, elevated risk of ASD was observed with infection in all trimesters. Finally, in the Stockholm Youth Cohort subsample, infection was more consistently associated with

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higher risk of ASD with intellectual disability as compared to ASD without intellectual disability.

Our study featured a number of strengths, including large well-characterized cohorts with validated ASD case ascertainment in the context of a socialized healthcare system; control for a number of covariates that suggest our results are not due to confounding by maternal psychiatric or somatic health, or contact with the healthcare system. Limitations included potential residual confounding from incomplete covariate control or uncontrolled confounding, although our sensitivity analysis suggested that such confounding is not likely to wholly explain our findings. In addition, prior validation efforts of infectious diseases in the National Patient Register have suggested varying data quality depending on the infectious condition. For example, in intensive care patients, ICD-9 diagnoses of CNS infection had a sensitivity of 95.4% and a specificity of 99.6%; in contrast, ICD-9 diagnoses of pneumonia had a sensitivity of 48.1% and a specificity of 95.9% (Gedeborg et al., 2007). Finally, while register-based diagnoses are objective and not subject to recall bias, no data were available regarding infections without an inpatient diagnosis. The incidence of infections in pregnant women is likely considerable. For example, 63.6% of women in the National Birth Defects Prevention Study self-reported having at least one infection during pregnancy (Collier et al., 2009). We were only able to consider maternal hospitalization with infection during pregnancy and could not investigate subclinical infections or infections treated by a general practitioner.

The results suggest that maternal hospitalization with infection during pregnancy may be associated with higher risk of ASD. A similar register-based study in Denmark of 10,000 ASD cases (Atladottir et al., 2010) found that maternal hospitalization for viral infection in the first trimester and any infection or bacterial infection in the second trimester were associated with risk. A recent study in California of 407 ASD cases and 2,075 controls found that maternal infection during a hospital admission, particularly bacterial infections, increased risk of ASD (Zerbo et al., 2013). While these studies also find evidence supporting an association between prenatal infection and ASD, our findings differ in several key areas. First, while the Atladottir et al. study highlights trimester-specific effects, our results suggest that increased risk due to infection may be observed in all trimesters. Second, our findings of increased risk with bacterial, viral, and other infections indicate a more generalized risk due to infection regardless of infectious agent.

The finding of generalized association (i.e., unspecific to bacterial, viral, or other infection) points toward unspecific disease processes underlying the associations rather than specific viruses with affinity to the brain parenchyma. Multiple animal models of prenatal infection have found evidence of diverse neurobehavioral abnormalities, whether through direct exposure of pregnant mice or rodents to influenza virus, or through non-infectious activation of the maternal immune system (e.g., using RNA poly(I:C) to stimulate an antiviral inflammatory response or lipopolysaccharide to stimulate a bacterial inflammatory response) (Brown and Derkits, 2010; Deverman and Patterson, 2009; Meyer et al., 2011; Miller et al., 2013; Patterson, 2011). The different pattern of associations observed for ASD with and without comorbid intellectual disability reinforces the possibility that higher-functioning and lower-functioning ASD may have different etiologies (Szatmari et al., 2007). For example,

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in an earlier study, we found that maternal use of antidepressants during pregnancy was associated with ASD without intellectual disability, but not with ASD with intellectual disability (Rai et al., 2013).

While individual infectious agents have unique characteristics (e.g., ability to cross the placenta, and potential for neurotropism) that could influence offspring risk potential for ASD, different infections may share common mechanisms on the biological pathway toward ASD risk. In particular, the hypothesis that cytokines may be involved in the etiology of schizophrenia and other neurodevelopmental disorders (Gilmore and Jarskog, 1997) appears particularly relevant to ASD. Numerous immune irregularities have been reported in children with ASD (Ashwood et al., 2011a; Ashwood et al., 2011b; Ashwood et al., 2006), especially with inflammatory cytokines. Cytokines are signaling molecules originally known for their role in the modulation of the immune system. However, cytokines also influence neuronal migration, axonal projections, synapse formation, and neuronal survival during development (Deverman and Patterson, 2009). Dysregulated levels of cytokines during development (e.g., due to maternal infections) therefore may adversely affect neurobehavioral function. In fact, recent studies suggest that dysregulated levels of various inflammatory markers in maternal sera (Goines et al., 2011) or amniotic fluid (Abdallah et al., 2011a, b) during pregnancy are associated with increased risk of ASD.

Although our study did not find evidence of differential ASD risk by trimester of exposure, changes in both innate and adaptive immune profiles over time during pregnancy are well-documented (Kraus et al., 2011). Also, developmental processes in the brain, such as cellular migration, axon generation and synapse formation occur in a sequential pattern and thus it is plausible that trimester-specific associations may have etiological implications. Animal models have demonstrated qualitatively different structural and functional phenotypes emerging after early- vs. late- gestation exposure to diverse immune challenges (as reviewed by (Meyer et al., 2007).

While the present study provides evidence that hospitalizations with a range of infections during pregnancy are associated with an increased risk of ASD, future work should investigate whether genetic pathways influence this environmental risk factor. For example, a number of studies have suggested the involvement of genetic factors influencing immune function in the etiology of ASD (Gregg et al., 2008; Voineagu et al., 2011). It is possible that such genetic involvement may act as a confounder (the genetic factor increases risk of both infection and ASD, resulting in a spurious association between infection and ASD) or as an instrument (the genetic factor increases risk of infection which then increases risk of ASD) or as an effect modifier (the genetic factor amplifies the deleterious effect of infection on risk of ASD) – but the latter two does not change the result that maternal infection is associated with ASD. Future studies considering variation in both genetic and environmental exposures will help to clarify the etiology of ASD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Acknowledgments

The authors would like to thank Henrik Dal, Lena Jorgensen, Michael Lundberg, and Susanne Wicks from the Division of Public Health Epidemiology, Department of Public Health Sciences at the Karolinska Institutet for their work on creating and reviewing the analytic datasets.

This study was funded by Autism Speaks grant number 7618 and Swedish Research Council grant 2012–2264. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Table 1

Selected characteristics of birth cohorts 1984–2007 of the total Swedish population and the Stockholm Youth Cohort subsample.

	Swedish population		Stockholm Youth Cohort subsample	
Characteristic, N (%)	**ASD cases (N = 24,414)**	**Non-cases (N = 2,346,989)**	**ASD cases (N = 9,585)**	**Non-cases (N = 487,408)**
Male (%)	17,062 (69.9)	1,200,355 (51.1)	6,808 (71.0)	247,884 (50.9)
Maternal age, mean years (SD)	28.8 (5.5)	29.0 (5.1)	29.8 (5.5)	29.9 (5.2)
Paternal age, mean years (SD)	32.0 (6.7)	31.8 (6.1)	32.8 (6.7)	32.8 (6.3)
Parity (%)				
1	11,024 (45.2)	976,634 (41.6)	4,594 (47.9)	216,570 (44.4)
2	7,900 (32.4)	852, 060 (36.3)	3,158 (33.0)	177,199 (36.4)
≥3	5, 490 (22.5)	518,295 (22.1)	1,833 (19.1)	93,639 (19.2)
Maternal history* of psychiatric care before delivery (%)	1,879 (7.7)	95,268 (4.1)	662 (6.9)	22,305 (4.6)
Maternal hospitalizations in the year prior to start of pregnancy				
0	19,363 (79.3)	1,945,116 (82.9)	7,741 (80.8)	402,698 (82.6)
1	3,944 (16.2)	329,833 (14.1)	1,495 (15.5)	71,808 (14.7)
2	775 (3.2)	54,627 (2.3)	247 (2.6)	10,093 (2.1)
≥3	332 (1.4)	17,413 (0.7)	102 (1.1)	2,809 (0.6)
Household income quintile (%)				
1 (Lowest)	4,427 (18.1)	361,066 (15.4)	1,485(15.5)	71,425 (14.7)
2	5,715 (23.4)	490,876 (20.9)	2,325 (24.3)	100,527 (20.6)
3	5,187 (21.3)	498,601 (21.2)	2,211 (23.1)	104,615 (21.5)
4	4,831 (19.8)	499,835 (21.3)	1,922 (20.1)	105,590 (21.7)
5 (Highest)	4,254 (17.4)	496,611 (21.2)	1,642 (17.1)	105,251 (21.6)
Region of birth of mother (%)				
Sweden	20,711 (84.8)	1,994,672 (85.0)	7,374 (76.9)	371,105 (76.1)
In Europe, outside Sweden	1,736 (7.1)	159,771 (6.8)	865 (9.0)	40,655 (8.3)
Outside Europe	1,966 (8.1)	192,482 (8.2)	1,346 (14.0)	75,642 (15.5)

* Includes both inpatient and partial outpatient data

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Table 2

Odds ratios and 95% CI of maternal hospitalization with infection during pregnancy and autism spectrum disorders in birth cohorts 1984–2007 in the Swedish population.

	N, ASD / non-ASD	OR (95% CI)
Unexposed	**23,511 / 2,285,347**	**1 (Reference)**
Any inpatient diagnosis		
Any infection	903 / 61,642	**1.37 (1.28, 1.47)**
Bacterial	574 / 37,950	**1.38 (1.27, 1.50)**
Viral	161 / 8,980	**1.54 (1.31, 1.81)**
Other	189 / 15,924	**1.22 (1.05, 1.41)**
Site-specific		
CNS	7 / 549	1.14 (0.54, 2.42)
Gastrointestinal	75 / 5,502	1.21 (0.96, 1.52)
Genitourinary	68 / 5,107	1.12 (0.88, 1.44)
Respiratory	88 / 5,992	**1.32 (1.07, 1.64)**
Skin	20 / 1,245	1.46 (0.93, 2.27)

Odds ratios and 95% CI are estimated from logistic regression models with clustered robust standard errors. The reference group for each OR is mothers without any inpatient diagnosis of infection during pregnancy. Modelsare adjusted for maternal age, paternal age, birth parity, birth year, sex of child, household income quintile, maternal country of origin, maternal history of psychiatric services prior to start of pregnancy, and maternal hospitalizations in the year prior to start of pregnancy

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Table 3

Trimester-specific odds ratios (95% CI) of maternal hospitalization with infection and autism spectrum disorders in birth cohorts 1984–2007 in the Swedish population.

	Trimester 1	Trimester 2	Trimester 3
Any inpatient diagnosis			
Any infection	**1.24 (1.00, 1.55)**	**1.38 (1.19, 1.61)**	**1.36 (1.26, 1.47)**
Bacterial	1.29 (0.96, 1.73)	**1.44 (1.19, 1.74)**	**1.38 (1.25, 1.52)**
Viral	**1.84 (1.17, 2.89)**	1.24 (0.80, 1.93)	**1.48 (1.23, 1.78)**
Other	0.86 (0.54, 1.35)	**1.39 (1.02, 1.88)**	**1.21 (1.01, 1.44)**

Logistic regression models with clustered robust standard errors are adjusted for other trimester-specific hospitalizations with infection, maternal age, paternal age, birth parity, birth year, sex of child, household income quintile, maternal country of origin, maternal history of psychiatric services prior to start of pregnancy, and maternal hospitalizations in the year prior to start of pregnancy.

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Table 4

Adjusted odds ratios and 95% CI of maternal hospitalization with infection during pregnancy and high- and low-functioning autism spectrum disorders in the Stockholm Youth Cohort subsample.

SYC subsample	ASD without intellectual disability		ASD with intellectual disability	
	N, ASD / non-ASD	OR (95% CI)	N, ASD / non-ASD	OR (95% CI)
Unexposed	6,888 / 471,056	1 (Reference)	2,280 / 471,056	1 (Reference)
Any inpatient diagnosis				
Any infection	293 / 16,352	**1.19 (1.06, 1.34)**	124 / 16,352	**1.50 (1.25, 1.81)**
Bacterial	190 / 10,546	**1.18 (1.02, 1.36)**	81 / 10,546	**1.47 (1.17, 1.85)**
Viral	42 / 2,297	1.22 (0.89, 1.66)	21 / 2,297	**1.61 (1.03, 2.54)**
Other	63 / 3,840	1.12 (0.87, 1.44)	26 / 3,840	**1.49 (1.01, 2.20)**
Site-specific				
CNS	0 / 184	-	1 / 184	-
Gastrointestinal	20 / 1,123	1.11 (0.71, 1.73)	9 / 1,123	1.51 (0.78, 2.91)
Genitourinary	15 / 1,051	0.96 (0.58, 1.60)	5 / 1,051	0.87 (0.36, 2.10)
Respiratory	28 / 1,311	**1.46 (1.00, 2.13)**	11 / 1,311	1.56 (0.86, 2.84)
Skin	6 / 276	1.52 (0.67, 3.43)	1 / 276	-

Logistic regression models with clustered robust standard errors are adjusted for maternal age, paternal age, birth parity, birth year, sex of child, household income quintile, maternal country of origin, maternal history of psychiatric services prior to start of pregnancy, and maternal hospitalizations in the year prior to start of pregnancy. Estimates with insufficient N of exposed cases (N < 5) are not shown.

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Table 5

Sensitivity of model results to unobserved confounding at specified parameter levels.

Increase in risk of ASD on account of unmeasured confounder*	Prevalence of unmeasured confounder in exposed	Prevalence of unmeasured confounder in unexposed	Adjusted OR (95% CI)
-	0	0	1.37 (1.28, 1.47)**
Doubled	10%	5%	1.31 (1.22, 1.40)
Doubled	20%	5%	1.20 (1.12, 1.29)
Doubled	30%	10%	1.16 (1.08, 1.24)
Doubled	40%	10%	1.08 (1.01, 1.16)
Doubled	50%	5%	0.96 (0.90, 1.03)
Tripled	10%	5%	1.26 (1.17, 1.35)
Tripled	20%	5%	1.08 (1.01, 1.16)
Tripled	30%	10%	1.03 (0.96, 1.10)
Tripled	40%	10%	0.91 (0.85, 0.98)
Tripled	50%	5%	0.75 (0.70, 0.81)

* assuming that the elevated risk of ASD due to *U* is consistent in both the exposed and the unexposed

** the original Table 2, Study 1 estimate of the OR for hospitalization with infection during pregnancy and risk of ASD in the total Swedish population