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# Infection in the First 2 Years of Life and Autism Spectrum Disorders

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## ABSTRACT

**OBJECTIVE.** The purpose of this work was to investigate the association between infections in the first 2 years and subsequent diagnosis of autism spectrum disorders.

**METHODS.** We conducted a case-control study among children born at Kaiser Permanente Northern California from 1995 to 1999. Case subjects ( $n = 403$ ) were children with an autism diagnosis recorded in Kaiser Permanente databases. Control subjects ( $n = 2100$ ) were randomly sampled from the remaining children without autism and frequency matched to case subjects on gender, birth year, and birth hospital. Information on infections and covariates were obtained from Kaiser Permanente and birth certificate databases.

**RESULTS.** Overall, infection diagnoses in the first 2 years of life were recorded slightly less often for children with autism than control children (95.0% vs 97.5%). Among specific diagnoses, upper respiratory infections were significantly less frequently diagnosed and genitourinary infections more frequently diagnosed in children with autism. In the first 30 days of life, the frequency of having an infection was slightly higher among children with autism (22.6% vs 18.7%).

**CONCLUSIONS.** Children with subsequent diagnoses of autism do not have more overall infections in the first 2 years of life than children without autism. Data suggest that children with autism may have modestly elevated rates of infection in the first 30 days and that, during the first 2 years, children with autism may be at higher risk for certain types of infections and lower risk for others. Additional studies that explore the associations between prenatal and early childhood infections and autism may help clarify the role of infection and the immune system in the etiology of autism spectrum disorder.

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### Key Words

autism, autistic disorder, infant, newborn  
infection, epidemiology

### Abbreviations

ASD—autism spectrum disorder  
Th—T helper  
KP—Kaiser Permanente  
ICD-9-CM—*International Classification of Diseases, Ninth Revision, Clinical Modification*  
OR<sub>a</sub>—adjusted odds ratio  
CI—confidence interval  
URI—upper respiratory tract infection  
UTI—urinary tract infection

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**A**UTISM SPECTRUM DISORDERS (ASDs) are common neurodevelopmental disorders characterized by impairments in social interaction, abnormalities in verbal and nonverbal communication, and restricted, stereotyped interests and behaviors.<sup>1</sup> Autism is more common in boys, occurring 4 times as often as in girls, and is typically diagnosed between ages 3 and 5 years.<sup>2</sup> Data published in the last few years suggest that autistic disorder occurs in 1 to 2 per 1000 births,<sup>3,4</sup> but the prevalence of the broader autism spectrum is ~4 to 6 per 1000.<sup>5,6</sup> The etiology of autism is not well understood. Twin and family studies indicate a strong genetic component,<sup>2</sup> and results from genetic studies suggest that autism may result from multiple genes acting in combination.<sup>7</sup> Current thinking is that exposure to environmental factors at critical periods of development in genetically susceptible individuals may contribute to occurrence and phenotypic expression.

Immune system disturbances have been widely reported in persons affected by autism. Findings include a decreased response to T-cell mitogens,<sup>8,9</sup> reduction of natural killer cell activity,<sup>10</sup> selective depletion of CD4<sup>+</sup> T-helper (Th)/inducer cells,<sup>9</sup> alterations in Th1 and Th2 responses,<sup>11,12</sup> increased numbers of DR<sup>+</sup> T cells,<sup>13</sup> and an imbalance of serum immunoglobulins and cytokines<sup>14</sup> in persons with ASD. Other studies have found that a higher percentage of persons with autism have anti-brain autoantibodies.<sup>15-17</sup> Most of these studies were conducted in older children, and the relevance of study findings to the perinatal and early childhood periods is not yet understood. However, if a dysregulated immune system is part of the pathology of autism, then children with autism could be more susceptible to infections early in life.

Some research suggests that prenatal<sup>18,19</sup> and early infantile infections<sup>20,21</sup> adversely affect brain development and may result in neuropsychiatric disorders.<sup>22</sup> However, there is very little published research that specifically investigates the association between early childhood infections and ASD. Many parents have anecdotally suggested that their children with ASD have higher rates of ear infections and antibiotic treatments during the period leading up to their child's diagnosis of autism compared with typically developing children. One small study of 42 children with autism in Canada found higher rates of ear infections, hearing loss, and ear drainage through tubes in children with autism than with their typically developing peers.<sup>23</sup> A Swedish study reported higher rates of ear infections, hyperacusia, and conductive hearing loss in children with autism compared with matched peers.<sup>24</sup> There have been a few case reports of the onset of autism or autistic-like symptoms after herpes simplex encephalitis infections<sup>25-29</sup> and cytomegalovirus infections.<sup>30-33</sup> Other studies have found an association of autism with congenital rubella.<sup>34,35</sup> One small case-control study of children with autism and

their unaffected siblings found that mumps, chickenpox, fever of unknown origin, and ear infections were associated with autism, although the overall exposure rates were low, suggesting that these infections were unlikely to play a role in a large proportion of autism cases.<sup>36</sup> Animal studies of Lewis rats infected with neonatal Borna disease virus have displayed behavioral abnormalities similar to autism.<sup>37,38</sup>

We undertook this study to evaluate the relationship between the frequency and types of infections diagnosed in the first 2 years of life and subsequent diagnosis of ASD in a large, well-defined, insured population in the United States. An association, if found, may indicate that early childhood infections and ASD share a common etiology, that infections are a causative factor for ASD, or that the timing of exposure to infection could be a causative factor for ASD.

## METHODS

We conducted a case-control study nested within a cohort of infants born alive between January 1995 and June 1999 at Kaiser Permanente (KP) in the northern California region who remained members of the KP health plan for  $\geq 2$  consecutive years after birth ( $n = 88\ 163$ ). KP is an integrated, group model, nonprofit health plan serving  $>3$  million members in northern California, representing 30% of the insured population in the area.

Our initial pool of case subjects was defined as children with an ASD diagnosis recorded in the KP outpatient databases, that is, autism (*International Classification of Diseases, Ninth Revision, Clinical Modification*<sup>39</sup> [ICD-9-CM] code 299.0), Asperger's syndrome (ICD-9-CM code 299.8), or pervasive developmental disorder not otherwise specified (ICD-9-CM code 299.9) at any time between January 1995 and December 2002 ( $n = 420$ ). For each case, 5 randomly selected control subjects were chosen from among the remaining study cohort and frequency matched by gender, birth year, and regional birth hospital within the KP system, resulting in a control sample of children without an ASD diagnosis ( $n = 2100$ ). Our final case group was limited to children who received their ASD diagnosis after age 2 ( $n = 403$ ).

Information on infections was derived from KP clinical databases, which prospectively capture all of the diagnoses made during inpatient, outpatient, emergency, and referral visits for KP members based on the ICD-9-CM coding system. We focused on infections diagnosed in the first 2 years of life, the period before the initial diagnosis of ASD for our cases, to reduce potential bias in infection reporting that could result from increased health care use (parental concern and more frequent visits to the doctor) once a child is diagnosed with ASD. Infection diagnoses were grouped into 12 mutually exclusive categories according to the schema provided in the ICD-9-CM as follows: bacterial, viral,

mycoses/ear, upper respiratory, lower respiratory, gastrointestinal, genitourinary, lymph node, skin, eye, and perinatal (those occurring in the neonate). Specific ICD-9-CM codes included in each category are displayed in Table 1. For each study child, we determined the total number of infections diagnosed within each infection category. To prevent counting the same infectious episode more than once, we used the typical duration for each type of infection plus a grace period to establish a minimum number of days after an initial diagnosis after which an infection from the same category was counted as a new infection (see Table 1).

Age at time of infection was categorized into 4 distinct time periods: (1) first 30 days; (2) 31 days to 6 months; (3) 7 to 12 months; and (4) 13 to 24 months. Demographic factors, including maternal age and education level at delivery, maternal race/ethnicity (white non-Hispanic, Hispanic, Asian, black, or other), plurality (singleton or multiple), and parity (number of previous live births) were ascertained from the California birth certificate files, which were electronically linked to the KP birth cohort. Information on birth order (first, second, third, or higher), birth weight, and gestational age was ascertained from KP clinical databases. Hospitalization codes in the KP databases were used to determine the frequency of hospitalizations during an infectious episode.

Differences between cases and controls in the frequency of early childhood infections and covariates were evaluated using a  $\chi^2$  test. Logistic regression<sup>40</sup> was performed to estimate the risk of ASD associated with early childhood infection before and after adjusting for the following covariates: gestational age, plurality, birth order, maternal age, maternal race/ethnicity, and maternal education. These variables were included in the multivariable models because they have been shown in previous studies to be associated with autism<sup>41–43</sup> and/or

early childhood infection.<sup>44,45</sup> Statistical significance was evaluated without correction for multiple comparisons, because we were interested in identifying all of the possible associations between the characteristics in question and ASD.

All of the infection categories were modeled as dichotomous variables (any versus none). To evaluate the association between frequency of overall infections and autism risk, we grouped the total number of infections into quartiles based on the frequency distribution among controls (1–4 infections, 5–7 infections, 8–12 infections, and >13 infections). To further assess autism risk associated with frequency of infection within any given category, a categorical variable (1 infection, 2–4 infections, and  $\geq 5$  infections) was defined for specific infection categories in which >50% of both case and control children had  $\geq 1$  diagnosed infection. The reference groups for these analyses were children with no recorded infections in that specific category.

Data from the KP databases were analyzed without personal identifiers by Kaiser staff under Health Insurance Portability and Accountability Act guidelines. Individual consent was not obtained by subjects, because there was minimal risk to study subjects and their families, no information was needed from the subjects or their families, and results have no direct clinical relevance to study subjects. In addition, obtaining consent would have been cost-prohibitive and would have yielded a more selective study population. All of the study procedures were approved by the KP Northern California Institutional Review Board and the California State Committee for the Protection of Human Subjects.

## RESULTS

Within the case group, 31% received their initial ASD diagnosis between the second and third birthday, and 69% received the diagnosis after the third birthday. De-

**TABLE 1** Infection Categories, ICD-9-CM Codes, Infection Durations, and Cutoff Periods

Infection Categories	ICD-9-CM Codes	Usual Duration, d	Counted as New Infection After No. of Days <sup>a</sup>
Gastrointestinal	001–009, 535, 567	5–7	>14
Bacterial	010–018, 020–027, 030–041, 320–322	2–14	>30
Viral	042, 045–049, 050–057, 060–066, 070–077, 078.2–079, 080–088, 090–099	7–10	>30
Skin	078.0, 078.1, 680–682, 684–686	7–10	>14
Mycoses	110–118	5–30	>30
Lymph	289.1–289.3, 683	21–30	>30
Eye	372	2–5	>7
Ear <sup>b</sup>	380, 381, 382	1–4	>14
Upper respiratory	460–465, 472, 473, 476, 487	7–14	>21
Lower respiratory	466, 480–486, 490, 491	7–14	>21
Genitourinary	590, 599.0, 616	2–7	>30
Perinatal	770.0, 771	21–30	>30

<sup>a</sup> To prevent double counting of the same infection, a minimum period was determined during which an infection from the same category was not counted more than once.

<sup>b</sup> Of the ear infections, 95% were otitis media.

mographic characteristics of the study population are shown in Table 2. Eighty-two percent of both case and control subjects were boys because of matching on gender. Children with ASD were more likely to be multiple births, born at an earlier gestation, and to weigh less at birth than children without ASD. Mothers of children with ASD were more likely to be older at delivery, white non-Hispanic, and have more years of education than control mothers.

The vast majority of case and control subjects had  $\geq 1$  infection recorded in the first 2 years of life (95.0% vs 97.4%; adjusted odds ratio [OR<sub>a</sub>]: 0.54; 95% confidence interval [CI]: 0.31–0.95; Table 3). The mean number of infections was similar for case and control subjects (8.7 vs 8.9;  $P = .60$ ), as was the mean number of infections among children who had  $\geq 13$  infections (18.4 vs 17.9;  $P = .33$ ).

Crude and OR<sub>a</sub> values for the specific infection categories are shown in Table 4. Upper respiratory infections (URIs) and ear infections were the most common infections diagnosed in both case and control children. Contrary to expectations, URIs (mainly nasopharyngitis, pharyngitis, croup, acute URI not otherwise specified, and sinusitis; OR<sub>a</sub>: 0.70; 95% CI: 0.50–0.97) were significantly less common among children with ASD. Ear infections (mainly otitis media; OR<sub>a</sub>: 0.77; 95% CI: 0.60–1.0) and lower respiratory infections (mainly bronchiolitis, pneumonia, and bronchitis; OR<sub>a</sub>: 0.85; 95% CI: 0.67–1.1) were also lower in case children, although results did not reach conventional levels of

statistical significance. The risk of ASD did not vary by total number of infections diagnosed in any of these categories.

Genitourinary infections (mainly urinary tract infections [UTIs]; OR<sub>a</sub>: 2.3; 95% CI: 1.3–4.4), were diagnosed twice as often in children later diagnosed with ASD than control subjects. Gastrointestinal infections (mostly viral enteritis and gastritis; OR<sub>a</sub>: 1.9; 95% CI: 0.91–4.1) and lymph infections (mainly lymphadenitis; OR<sub>a</sub>: 2.2; 95% CI: 0.75–6.6) were observed more frequently in children with ASD, but the results did not reach statistical significance. These infections occurred among different children, and the results cannot be attributed to a few sick children who had multiple infections. There were no significant case-control differences in the frequency of bacterial, viral, skin, mycosal, or eye infections diagnosed in the first 2 years of life or in perinatal infections diagnosed in the neonate (neonatal candida, conjunctivitis and omphalitis, and perinatal infections not elsewhere classified).

Specific viral infections were also examined. None of the study children had a recorded diagnosis of measles, mumps, or rubella in the first 2 years of life. A similar proportion of case and control subjects had a diagnosis of varicella (1.7% vs 1.4%;  $P = .65$ ). One child in the control group had a diagnosis of cytomegalovirus, and 1 case and 16 control children had a recorded herpes infection during the first 2 years of life (0.02% vs 0.08%;  $P = .23$ ).

In the subset of case subjects ( $n = 151$ ) who were also enrolled with California Department of Developmental Services, a state service agency that is mandated to provide services to children with autistic disorder or children with ASD who are substantially handicapped, the rate of overall infections (96%) was similar to that reported above for the entire case group, as were the associations with ASD risk obtained for specific types of infections. The increased risk associated with genitourinary infections was somewhat attenuated (4.0% vs 1.8%; OR<sub>a</sub>: 2.3; 95% CI: 0.92–5.8) and that of gastrointestinal infections was slightly increased (3.3% vs 1.3%; OR<sub>a</sub>: 2.8; 95% CI: 1.0–7.5) compared with the association reported above for the overall case group. The decreased risk of ear infections (70.9% vs 78.4%; OR<sub>a</sub>: 0.71; 95% CI: 0.48–1.0) was also slightly stronger in this subset of case subjects compared with the whole. Analyses of bacterial, viral, skin, mycosal, lymph, eye, ear, and upper and lower respiratory tract infections for this subset of case subjects yielded similar results to those observed for the entire case group.

Among children with  $\geq 1$  documented infection in the first 2 years of life (383 case subjects and 2048 control subjects), children with ASD were hospitalized for infections slightly more often than control children, but differences were not statistically significant (10.7% vs 8.4%; OR<sub>a</sub>: 1.3; 95% CI: 0.90–1.9; Table 5). The

**TABLE 2** Description of the Study Population: KP Births Occurring January 1995 to June 1999

Characteristic	ASD Cases ( <i>n</i> = 403)	Controls ( <i>n</i> = 2100)	<i>P</i>
Gender, <i>n</i> (%)			NA
Female	77 (18.3)	387 (18.4)	
Male	343 (81.7)	1713 (81.6)	
Plurality, <i>n</i> (%)			<.001
Singleton	385 (91.7)	2032 (96.7)	
Multiple	34 (8.1)	60 (2.9)	
Unknown	1 (0.2)	8 (0.38)	
Maternal education, <i>n</i> (%)			<.001
<High school graduate	21 (5.0)	208 (9.9)	
High school graduate	81 (19.3)	603 (28.7)	
Undergraduate college	233 (55.5)	995 (47.4)	
Postgraduate	82 (19.5)	261 (12.4)	
Unknown	3 (0.7)	33 (1.6)	
Maternal race/ethnicity, <i>n</i> (%)			.02
White, non-Hispanic	216 (51.4)	948 (45.1)	
White, Hispanic	66 (15.7)	477 (22.7)	
Black	36 (8.6)	188 (9.0)	
Asian	46 (11.0)	218 (10.4)	
Other	56 (13.3)	269 (12.8)	
Maternal age, mean (SD), y	31.2 (5.4)	29.8 (5.7)	<.001
Gestational age, mean (SD), wk	38.8 (2.3)	39.1 (1.9)	<.001
Birth weight, mean (SD), g	3395.6 (675.5)	3471.6 (597.9)	.02

NA indicates not applicable because of matching.

**TABLE 3 Overall Number of Infections in First 2 Years of Life**

Infections	ASD Cases (n = 403)		Controls (n = 2100)		OR <sub>c</sub> (95% CI)	OR <sub>a</sub> (95% CI)
	n	%	n	%		
None	20	5.0	52	2.5	Ref	—
Any	383	95.0	2048	97.5	0.5 (0.3–0.9)	0.54 (0.31–0.95)
1–4	105	26.0	532	25.3	Ref	—
5–7	73	22.9	454	21.6	1 (0.77–1.4)	1.1 (0.81–1.5)
8–12	88	21.9	556	26.5	0.8 (0.6–1.1)	0.83 (0.6–1.1)
≥13	97	24.1	506	24.1	0.98 (0.72–1.3)	1.1 (0.77–1.4)

OR<sub>a</sub> indicates OR<sub>a</sub> for maternal age, maternal race, maternal education, gestational age, birth order, and plurality; OR<sub>c</sub>, crude OR; Ref, reference group.

majority of hospitalizations were because of ear infections for both case subjects (84%) and control subjects (88%). We compared the rates of diagnosed infection between case and control children within 4 distinct time periods (birth to 30 days, 31 days to 6 months, 7–12 months, and 13–24 months; Fig 1). The rate of infection increased over the first 2 years of life, and the greatest number of children (case and control subjects) were diagnosed with infections between 13 and 24 months of age. The only time period with a significant case-control difference was the first 30 days of life, during which time a significantly greater proportion of children later identified with ASD were diagnosed with an infection (22.6% vs 18.7%;  $P = .03$ ; OR<sub>a</sub>: 1.4; 95% CI: 1.1–1.7).

## DISCUSSION

We found little difference between children with and without ASD in the overall rate of infections diagnosed in the first 2 years of life. If anything, children with ASD had slightly lower overall rates of infections than control subjects in the first 2 years. However, in the first month of life, children who would later receive an ASD diagnosis were more likely to be diagnosed with an infection. Among 12 distinct categories of infections, genitourinary infections were somewhat more commonly diagnosed in children with ASD, as well as the subset who were receiving California Department of Developmental Services services, and, thus, were presumably more severely affected. Contrary to what we expected, these data suggest that children with ASD may have slightly lower rates of ear infections and URIs in the first 2 years of life than children without ASD.

To our knowledge, this study reports the first comprehensive investigation of the frequency and timing of infections in early childhood among children with ASD. Our findings are strengthened by the use of a large study sample, which provided adequate power to detect differences in the rate and timing of all types of infections occurring in the first 2 years of life. Unlike other studies that relied on maternal report of childhood infection history, this study defined infection history based on physician-documented diagnoses prospectively recorded

in medical charts. We also had extensive information on several important covariates and performed multivariable analyses to adjust for potential confounding.

The demographic profile of KP members is very similar to the 14-county catchment area served by KP in northern California, with the exception of the very poor and very wealthy, who are underrepresented.<sup>46</sup> The demographic characteristics of our case population are similar to previously published articles on the characteristics of children with autism in California.<sup>41</sup> In addition, our control group was randomly selected from the same population from which the case subjects arose. Because we matched case and control subjects by hospital of birth, it is likely that case and control subjects lived in similar geographic areas around the time of birth.

It should be noted that the rates of specific infections in our control population were somewhat higher than previously published rates. For example, ear infections were diagnosed in 78% of our control children in comparison with published prevalence rates for otitis media of 69% to 71% in young children.<sup>47,48</sup> UTIs were diagnosed in 1.6% of our control subjects compared with estimated prevalence rates ranging from 0.3% to 1.2% in children ≤2 years old.<sup>49</sup> These higher rates may suggest that children seen in the KP system may be more likely to visit doctors for common infections or that KP physicians conduct rigorous screening practices.

This study has several limitations that deserve mention. First, the study population was restricted to children who were KP members for ≥2 consecutive years after birth, and, thus, our results may not be generalizable to children without health insurance or those who switch insurers before their second birthday. ASD diagnoses were not validated by a standardized clinical assessment. However, for a sample of 198 case children, detailed information on diagnoses, school services, behavioral and developmental history, and psychometric assessment results was abstracted from all of the pediatric and mental health records following a protocol initially developed by the Metropolitan Atlanta Developmental Disabilities Surveillance Program<sup>6</sup> and adapted by the Centers for Autism and Developmental Disabilities Research and Epidemiology. A child psychiatrist

**TABLE 4 Infections in First 2 Years of Life According to Type of Infection**

Exposure	ASD Cases (n = 403)		Controls (n = 2100)		OR <sub>c</sub> (95% CI)	OR <sub>a</sub> (95% CI)
	n	%	n	%		
Gastrointestinal						
None	393	97.5	2072	98.7	Ref	—
Any	10	2.5	28	1.3	1.8 (0.91–3.9)	1.9 (0.91–4.1)
Bacterial						
None	388	96.3	2038	97.0	Ref	—
Any	15	3.7	62	3.0	1.4 (0.80–2.4)	1.3 (0.7–2.3)
Viral						
None	145	36.0	830	39.5	Ref	—
Any	258	64.0	1270	60.5	1.1 (0.92–1.4)	1.1 (0.90–1.4)
1	151	37.5	694	33.1	1.2 (0.97–1.5)	1.2 (0.78–1.4)
2–4	102	25.3	555	26.4	1 (0.78–1.3)	1 (0.78–1.4)
≥5	5	1.3	21	1.0	1.5 (0.62–3.9)	1.4 (0.52–3.6)
Skin						
None	350	86.9	1828	87.0	Ref	—
Any	53	13.1	272	13.0	0.99 (0.59–1.4)	1 (0.76–1.4)
Mycoses						
None	302	74.9	1571	74.8	Ref	—
Any	101	25.1	529	25.2	1.1 (0.83–1.4)	1 (0.78–1.3)
Lymph						
None	398	98.8	2087	99.4	Ref	—
Any	5	1.2	13	0.6	2.3 (0.88–6.15)	2.2 (0.75–6.6)
Eye						
None	258	64.0	1279	60.9	Ref	—
Any	145	35.0	821	39.1	0.87 (0.70–1.1)	0.87 (0.69–1.1)
Ear						
None	112	27.8	453	21.6	Ref	—
Any	291	72.1	1647	78.4	0.74 (0.58–0.94)	0.77 (0.60–1.0)
1	69	17.1	464	22.1	0.63 (0.46–0.87)	0.65 (0.47–0.90)
2–4	144	35.7	732	34.9	0.81 (0.62–1.1)	0.89 (0.67–1.2)
≥5	78	19.6	451	21.5	0.72 (0.53–0.99)	0.8 (0.57–1.1)
URI						
None	59	14.6	210	10.0	Ref	—
Any	344	85.4	1890	90.0	0.65 (0.48–0.88)	0.7 (0.50–0.97)
1	62	15.4	329	15.7	0.67 (0.45–1.0)	0.72 (0.48–1.10)
2–4	162	40.2	992	47.2	0.58 (0.42–0.81)	0.61 (0.44–0.87)
≥5	120	29.8	569	27.1	0.75 (0.53–1.1)	0.84 (0.58–1.2)
Lower respiratory infection						
None	281	69.7	1379	65.7	Ref	—
Any	122	30.3	721	34.3	0.83 (0.66–1.0)	0.85 (0.67–1.1)
Genitourinary						
None	387	96.0	2063	98.2	Ref	—
Any	16	4.0	37	1.8	2.2 (1.2–4.0)	2.3 (1.3–4.4)
Perinatal						
None	368	91.3	1976	94.1	Ref	—
Any	35	8.7	134	6.4	1.4 (0.95–2.1)	1.3 (0.90–2.0)

OR<sub>a</sub> indicates OR<sub>a</sub> for maternal age, maternal race, maternal education, gestational age, birth order, and plurality; OR<sub>c</sub>, crude odds ratio; Ref, reference group.

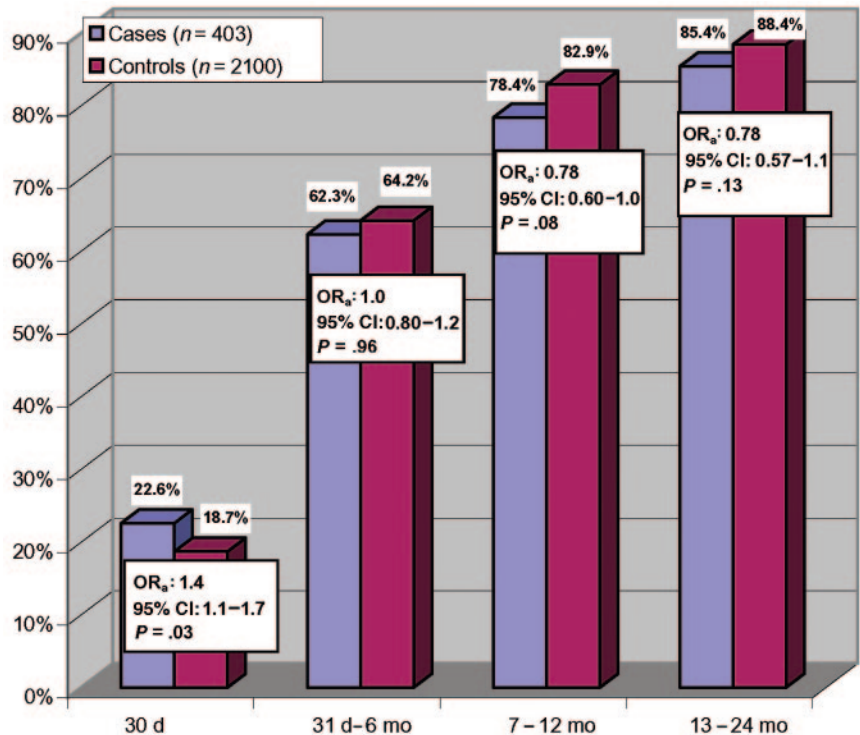
**TABLE 5 Comparison of Rates of Hospitalizations During an Infectious Episode**

Hospitalizations	ASD Cases (n = 383)		Controls (n = 2048)		OR (95% CI) <sup>c</sup>	OR <sub>a</sub> (95% CI)
	n	%	n	%		
None	342	89.3	1877	91.6	Ref	—
Any	41	10.7	171	8.4	1.3 (0.91–1.9)	1.3 (0.90–1.9)
1	34	8.9	147	7.2	1.3 (0.86–1.9)	1.3 (0.86–1.9)
≥2	7	1.8	25	1.2	1.7 (0.75–3.8)	1.4 (0.58–3.4)

OR<sub>a</sub> indicates OR<sub>a</sub> for maternal age, maternal race, maternal education, gestational age, birth order, and plurality; OR<sub>c</sub>, crude odds ratio; Ref, reference group.

with clinical expertise in autism reviewed the abstracted information and determined that 87% of children met criteria for ASD, and 7% were suspected to have ASD based on *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria and clinical impression. Of the remaining children, only 1% did not qualify as having ASD, and for 5% there was not adequate information in the chart to give a diagnosis. Because medical charts were not similarly reviewed for control children, it is possible that a small number of children who were, in fact, case subjects may have been misclassified as control subjects.

**FIGURE 1**  
 Percentage of children with and without ASD diagnosed with an infection in the first 2 years of life. OR<sub>s</sub> for maternal age, maternal race, maternal education, gestational age, birth order, and plurality.



Although the use of physician-documented infection diagnoses recorded in medical charts reduces the possibility of exposure misclassification because of recall bias, infections may have been underascertained. Parents may not have taken their children to the doctor for minor infections, including colds and ear infections, and these would not be recorded in the databases. Conversely, infections may have been overascertained in situations where diagnoses were recorded at follow-up visits for unusually prolonged illnesses. To bias results, documentation of infections in medical charts would have to be different for case and control subjects. Because some infection categories had higher and some had lower frequencies in children with ASD, it is unlikely that there is a systematic bias in exposure classification. It is also unlikely that parental concern, resulting in more frequent visits to the doctor, produced a systematic bias in exposure classification.

We did not have information on 2 important predictors of susceptibility to infections that may confound any observed association between ASD and infections during early childhood: breastfeeding and enrollment in day care. Two studies have compared breastfeeding rates among children with and without autism; 1 reported no difference,<sup>50</sup> and another found that children with autism were weaned earlier than controls.<sup>51</sup> To our knowledge, no formal studies have been conducted to compare the age of entry or length of time in day care among children with and without ASD in the first 2 years of life. We also did not have sufficient information to assess infection severity.

However, if infection-related hospitalizations were to serve as a proxy for severity, then our results suggest that infection severity was not associated with ASD risk.

The role of gastrointestinal disturbances and infections in children with ASD still needs more rigorous investigation. There have been many case reports and anecdotal accounts from parents of gastrointestinal disturbances among their autistic children, and some pediatric gastroenterologists have reported that 46% to 84% of children with ASD have gastrointestinal symptoms.<sup>52</sup> However, a recent review found that, because of the lack of systematic study, there is currently no scientific evidence supporting the hypothesis of elevated levels of gastrointestinal disturbances in ASD.<sup>53</sup> Although our study did find an elevated rate of gastrointestinal infections in children later diagnosed with ASD in a group of >400 cases, this result was not statistically significant at the .05 level.

To our knowledge, elevated risk of genitourinary infections in children with ASD has not been reported previously, although a few studies have reported increased rates of maternal urinary tract and vaginal infections during pregnancy.<sup>54,55</sup> Ninety-four percent of our cases with a genitourinary infection were diagnosed with a UTI. Risk factors for UTIs in infants and young children that were not controlled for in our analysis include having an uncircumcised penis,<sup>56</sup> the presence of associated infectious diseases, use of broad-spectrum antibiotics, renal and urinary tract malformations, mechanical ventilation, and prolonged stays in the ICU.<sup>57,58</sup>

A positive link of ASD with UTIs may indicate an association with  $\geq 1$  of these underlying risk factors. The lower rates of ear and upper and lower respiratory infections that we observed in this population were contrary to what we expected and may be because of chance. Another possible explanation is that children with ASD or at risk for ASD may be less likely to complain or exhibit signs of ear pain than children without ASD.

The observed association between ASD and infections in the first 30 days of life suggests that maternal infection during pregnancy may be etiologically relevant. Past studies have reported positive<sup>36,59</sup> and negative associations<sup>60</sup> of maternal infection during pregnancy and autism risk. Animal studies suggest a link between prenatal maternal viral infections and behavioral changes in the offspring,<sup>61</sup> as well as effects on the brain<sup>62</sup> and alterations in expression of brain genes,<sup>63</sup> producing behaviors and structural changes in the brain similar to findings observed in some autistic individuals. Other data suggest that maternal antibodies during pregnancy could adversely impact fetal brain development.<sup>64,65</sup> Future analysis of this data set will look at maternal infection during pregnancy and ASD risk.

Additional large epidemiological studies of early childhood infections in different populations are needed to clarify the association with ASD risk among children who share similar phenotypic traits. Future studies that include the collection of data on clinical infection history of mothers and children, as well as biological specimens from pregnancy, birth, and early childhood, for future testing of markers of infection and inflammation would be especially helpful in examining the immune system function related to infectious exposures.

## CONCLUSIONS

The findings from this large population-based case-control study suggest that infections in the first 2 years of life are no more common in children who are subsequently diagnosed with ASD than control children. Children with ASD may be more likely to have infections diagnosed in the first month of life and may also be at somewhat higher risk for certain types of infections, including genitourinary and gastrointestinal infections. Children with ASD may also have lower rates of other types of infections, specifically, ear and respiratory infections. However, these findings require replication in other study populations. Future studies should also compare patterns of treatment for infections and immune system responses to infection in children with and without ASD to shed light on the role of infection and immune system response in the etiology of autism.

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## Infection in the First 2 Years of Life and Autism Spectrum Disorders

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