

Association Between Influenza Infection and Vaccination During Pregnancy and Risk of Autism Spectrum Disorder

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[+ Supplemental content](#)

IMPORTANCE Maternal infections and fever during pregnancy are associated with increased risk for autism spectrum disorders (ASDs). To our knowledge, no study has investigated the association between influenza vaccination during pregnancy and ASD.

OBJECTIVE To investigate the association between influenza infection and vaccination during pregnancy and ASD risk.

DESIGN, SETTING, AND PARTICIPANTS This cohort study included 196 929 children born at Kaiser Permanente Northern California from January 1, 2000 to December 31, 2010, at a gestational age of at least 24 weeks.

EXPOSURES Data on maternal influenza infection and vaccination from conception date to delivery date, obtained from Kaiser Permanente Northern California inpatient and outpatient databases. Influenza infection was defined by the *International Classification of Diseases, Ninth Revision, Clinical Modification* codes or positive influenza laboratory test results.

MAIN OUTCOMES AND MEASURES Clinical diagnoses of ASDs identified by *International Classification of Diseases, Ninth Revision, Clinical Modification* codes 299.0, 299.8, or 299.9 recorded in Kaiser Permanente Northern California electronic medical records on at least 2 occasions any time from birth through June 2015.

RESULTS Within this cohort of 196 929 children, influenza was diagnosed in 1400 (0.7%) mothers and 45 231 (23%) received an influenza vaccination during pregnancy. The mean (SD) ages of vaccinated and unvaccinated women were 31.6 (5.2) and 30.4 (5.6) years, respectively. A total number of 3101 (1.6%) children were diagnosed with ASD. After adjusting for covariates, we found that maternal influenza infection (adjusted hazard ratio, 1.04; 95% CI, 0.68-1.58) or influenza vaccination (adjusted hazard ratio, 1.10; 95% CI, 1.00-1.21) anytime during pregnancy was not associated with increased ASD risk. In trimester-specific analyses, first-trimester influenza vaccination was the only period associated with increased ASD risk (adjusted hazard ratio, 1.20; 95% CI, 1.04-1.39). However, this association could be due to chance ($P = 0.1$) if Bonferroni corrected for the multiplicity of hypotheses tested ($n = 8$). Maternal influenza vaccination in the second or third trimester was not associated with increased ASD risk.

CONCLUSIONS AND RELEVANCE There was no association between maternal influenza infection anytime during pregnancy and increased ASD risk. There was a suggestion of increased ASD risk among children whose mothers received an influenza vaccination in their first trimester, but the association was not statistically significant after adjusting for multiple comparisons, indicating that the finding could be due to chance. These findings do not call for changes in vaccine policy or practice, but do suggest the need for additional studies on maternal influenza vaccination and autism.

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Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder with unknown causes in most cases. Previous studies suggest that genetic and environmental factors play a role in the etiology of ASD.¹⁻³

While some previous studies report no association between maternal infections during pregnancy and ASD risk,⁴⁻⁶ many recent epidemiological studies report an increased ASD risk in association with maternal infections⁷⁻¹¹ and fever during pregnancy.^{12,13} Some studies examine infection timing, but results have been mixed. First-trimester viral infection is associated with increased risk in some studies,^{7,9} while other studies report second- or third-trimester bacterial infection.^{7,9-11}

Influenza viruses are prevalent worldwide, and it is estimated that more than 200 000 people in the United States are hospitalized each year for respiratory and heart conditions, illnesses associated with seasonal influenza virus infections.¹⁴ Previous epidemiological studies on associations between influenza infection during pregnancy and ASD reported mixed results. While 2 previous studies found associations between maternal influenza and increased ASD risk,^{12,15} other studies did not.^{8,11,13} However, we found that children conceived in California during peak influenza infection months were at increased ASD risk.¹⁶ Small sample sizes did not allow most previous studies to examine the timing of influenza infection during pregnancy and ASD risk.

Influenza infection and influenza vaccination are associated with immune activation. Animal model studies show an association between maternal immune activation during pregnancy and behavioral and brain abnormality in offspring, similar to those observed in children with ASD.¹⁷⁻¹⁹ Pregnant women are encouraged to get vaccinated against influenza because they face an increased risk of complications from the infection.²⁰ Studies show that influenza vaccination during pregnancy reduces risk of a preterm birth, a small-for-gestational-age child, and a low-birth-weight child,^{21,22} and prevents influenza infection in newborns for up to 6 months.²³ However, to our knowledge, no study has investigated the association between maternal influenza vaccination during pregnancy and ASD risk. This study's objective is to evaluate the association between maternal influenza infection and vaccination during pregnancy and ASD risk in a large cohort of children born at Kaiser Permanente Northern California (KPNC).

Method

Study Population

The study population was drawn from the cohort of children born during the period from January 1, 2000, to December 31, 2010 at KPNC, an integrated health care delivery organization that provides health care to approximately 3.5 million residents (25%-30%) in metropolitan San Francisco and Sacramento and surrounding counties. Kaiser Permanente Northern California members are broadly socioeconomically representative of the population except for the extremes of income distribution.²⁴ Eligibility was restricted to singleton children who were born at a gestational age of at least 24 weeks and who remained health plan members until at least 2 years of age

Key Points

Question Is there an association between maternal influenza infection and vaccination and autism risk?

Findings In a cohort study of 196 929 children, of whom 3103 had autism spectrum disorder, maternal influenza infection during pregnancy was not associated with increased autism risk. There was a suggestion of increased risk of autism spectrum disorders among children whose mothers received an influenza vaccination during their first trimester, but the association was statistically insignificant after adjusting for multiple comparisons, indicating that the finding could be due to chance.

Meaning Our findings do not call for vaccine policy or practice changes but do suggest the need for additional studies.

(n = 196 929). Each study participant's mother was identified from KPNC electronic medical records and data on maternal exposures during pregnancy (eg, influenza infection and influenza vaccination), and covariates were extracted. The study protocol was approved by the KPNC institutional review board and the California State Committee for the Protection of Human Subjects, which waived written consent for participants because our data-only study had no direct contact with patients.

Maternal Influenza Infection and Influenza Vaccination

Data on influenza infection and vaccination during pregnancy were obtained from KPNC inpatient and outpatient databases. Influenza infection was defined by the presence of any 1 of the following in the mother's electronic medical record from conception date to delivery date: *International Classification of Diseases, Ninth Revision, Clinical Modification* codes 487, 078.8, 079.9, or 465.9 during the influenza season (from October 1 to April 30) or a positive laboratory result for influenza based on the Prodesse ProFlu+ Assay (Hologic), a multiplex real-time polymerase chain reaction in vitro diagnostic test. Maternal influenza vaccination was defined as receipt of an influenza vaccination from conception date to delivery date. Women who were dually exposed were considered exposed in each analysis.

Four periods of influenza infection and influenza vaccination exposure were defined: the first trimester (1-12 weeks after conception), the second trimester (13-28 weeks after conception), the third trimester (29 weeks after conception to the delivery date), and anytime during pregnancy (conception date to delivery date). The conception date was defined as the date of the mother's last menstrual period plus 14 days. Women exposed to multiple influenza infections or vaccinations were counted in each corresponding period.

Autism Spectrum Disorders

Autism spectrum disorders are defined by ASD diagnoses (autistic disorder, Asperger disorder, and pervasive development disorder, not otherwise specified [*International Classification of Diseases, Ninth Revision, Clinical Modification* codes 299.0, 299.8, 299.9, respectively]) recorded in KPNC's pediatric electronic medical records on at least 2 occasions from birth through June 30, 2015.

Covariates

Maternal and infant characteristics, obtained from KPNC prenatal and pediatric electronic medical records and state vital statistics databases, adjusted the measure of association between maternal influenza infection and vaccination during pregnancy and ASD risk in multivariate analyses. Covariates included the child's sex, calendar conception year (categorical variable), gestational age, maternal prepregnancy body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) (BMI < 18.5 = underweight; 18.5 ≤ BMI < 25 = normal weight; 25 ≤ BMI < 30 = overweight; BMI ≥ 30 = obese), maternal age at delivery (younger than 20, 20 to 24, 25 to 29, 30 to 34, and ≥ 35 years), maternal education at delivery (≤ high school graduate, some college education, college graduate, postgraduate, or unknown), maternal race/ethnicity (Asian, black, white, or other), and gestational diabetes (yes/no). Additional covariates included maternal asthma (yes/no), hypertension (yes/no), autoimmune disease (yes/no), and allergies (yes/no) recorded in the electronic medical record before the conception date. All covariates were chosen a priori because of their association with ASD in previous studies^{25,26} or because they are indications for influenza vaccination.

Data Analysis

To account for differential follow-up time until ASD could be diagnosed, we used a Cox proportional hazards regression model to separately estimate the association between maternal influenza infection or vaccination and ASD risk. We generated unadjusted Kaplan-Meier plots for ASD risk over time along with the numbers at risk at discrete periods among children of vaccinated and unvaccinated mothers. The hazard ratio (HR) can be interpreted as the risk ratio. The outcome of interest is ASD. The censoring date was either the date of last membership in the health plan if there was no ASD diagnosis, or the end of the study period, June 30, 2015. For each exposure, we conducted separate analyses for each period: the first trimester, the second trimester, the third trimester, and anytime during pregnancy. For each analysis, the unexposed reference group was defined as not having the exposure of interest at any time during pregnancy. In all multivariable analyses, we included all of the covariates already described plus the conception season (winter, fall, spring, and summer) to control for influenza infection and vaccination seasonality. Finally, we conducted a post hoc analysis to adjust for multiple comparisons using the Bonferroni correction and a sensitivity analysis to determine the effect of potential unmeasured confounders.

Results

This study included 196 929 children born between 2000 and 2010. Influenza vaccination among pregnant women in this cohort (45 231, 23%) increased from a low of 6% in 2000 to a high of 58% in 2010. Compared with unvaccinated pregnant women, vaccinated pregnant women were more likely to be older and have a college education. Asthma, autoimmune disease, and hypertension were more likely to be diagnosed in vac-

inated women before conception, and gestational diabetes was more likely to be diagnosed during the study pregnancy (Table 1). In the 0.7% (1400) of cases in which influenza was diagnosed in pregnant women, they were more likely to be younger than the women who did not have influenza. These women were also more likely to have the same health conditions as vaccinated pregnant women (eTable 1 in the Supplement). A small proportion of women were exposed to both influenza infection and influenza vaccination during pregnancy (0.2%).

Follow-up time was between 2 and 15 years (median, 8.3 years; 25th percentile, 5.8 years; 75th percentile, 11.4 years). By the end of the study, ASD was diagnosed in 3103 children (1.6%). Compared with children without ASD, children with ASD were more likely to be male and born at less than 37 weeks' gestation. Mothers of children with ASD were more likely to be older at delivery and have a college or postgraduate education. Asthma, autoimmune disease, and hypertension were more likely to be diagnosed in these women before conception, as well as gestational diabetes during the study pregnancy (Table 2).

After controlling for maternal and child covariates, we found that maternal influenza infection anytime during pregnancy was not associated with increased ASD risk (adjusted HR [AHR], 1.04 [95% CI, 0.68-1.58]). There was also no association between maternal influenza infection during the first, second, or third trimester and ASD risk (Table 3).

The unadjusted proportion of ASD was slightly higher throughout follow-up among children of women who received influenza vaccinations during pregnancy compared with children of unvaccinated women (Figure). After adjustment for covariates, maternal influenza vaccination anytime during pregnancy was not significantly associated with increased ASD risk (AHR, 1.10 [95% CI, 1.00-1.21]) (Table 3). After adjustment for covariates, first trimester influenza vaccination was associated with an increased risk of ASD (AHR, 1.20 [95% CI, 1.04-1.39], *P* = .01); however, adjusting for the multiplicity of hypotheses tested (*n* = 8) using the Bonferroni correction suggests that this association could be due to chance (*P* = .10). Maternal influenza vaccination in the second (AHR, 1.03 [95% CI, 0.91-1.18]) and third (AHR, 1.03 [95% CI, 0.90-1.20]) trimesters was not associated with increased ASD risk (Table 3).

In a sensitivity analysis, we found that if an unmeasured confounder increased the propensity of maternal influenza vaccination during the first trimester and ASD risk by 30%, then our observed HR of 1.2 associated with maternal vaccination in the first trimester could be attributed to a combination of bias and chance (eMethods and eTable 2 in the Supplement).

Discussion

Maternal influenza infection during pregnancy was not associated with increased ASD risk in this study, and the association did not vary by the timing of influenza infection. These results are similar to our previous findings and 2 recent studies of no association between influenza infection during preg-

Table 1. Characteristics of Vaccinated and Unvaccinated Pregnant Women Who Delivered Children Born at Kaiser Permanente Northern California, 2000-2010

Characteristic	Women, No. (%)		P Value
	Vaccinated (n=45 231)	Unvaccinated (n=151 698)	
Age, mean (SD), y	31.6 (5.2)	30.4 (5.6)	<.001
Education			
≤High school	8958 (19.8)	45 594 (30.1)	
Some college	11 414 (25.2)	44 649 (29.4)	
College graduate	13 869 (30.7)	34 003 (22.4)	<.001
Postgraduate	10 198 (22.6)	23 877 (15.7)	
Unknown	792 (1.8)	3575 (2.4)	
Race/ethnicity			
White	29 429 (65.1)	98 973 (65.2)	
Black	1851 (4.0)	11 939 (7.9)	<.001
Asian	12 326 (27.3)	34 961 (23.1)	
Other	1625 (3.6)	5825 (3.8)	
Gestational age, wk			
<37	2667 (5.9)	10 170 (6.7)	<.001
≥37	42 564 (94.1)	141 528 (93.3)	
BMI before pregnancy, mean (SD)	26.37 (5.60)	26.84 (5.51)	<.001
Gestational diabetes	4805 (10.6)	11 958 (7.9)	<.001
Maternal medical history before pregnancy			
Asthma	809 (1.8)	1725 (1.1)	
Autoimmune disease	1195 (2.6)	2569 (1.7)	
Allergy	2198 (4.9)	5569 (3.7)	<.001
Hypertension	436 (1.0)	948 (0.6)	

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

nancy and ASD risk.^{8,10,11,13} Our previous 2 studies were limited by small sample sizes and possible recall bias, which were addressed in this study by using a larger sample size and electronic medical records. Our results are different from the results in the small case-control study by Deykin and MacMahon.¹⁵ They are also different from the results of Atladóttir and colleagues,¹² which were based on self-reported influenza infection data collected from women shortly after they became pregnant. Our study population included outpatient and inpatient influenza data with physician-documented influenza diagnoses.

Self-reported infection data may be affected by overcounting or undercounting, depending on severity and the mothers' health care access and care-seeking behavior. A poor agreement has been reported between hospital admission data and self-reported respiratory illnesses, particularly influenza infection.¹² However, it is possible that medical records may undercount influenza infections because some physicians discourage patients from seeking their services for viral infections. We do not expect physicians' behavior in influenza treatment to differ with respect to child outcome, and thus our results may be biased toward the null.

We found that influenza vaccination in the first trimester was associated, in an initial analysis unadjusted for multiple comparisons, with a slightly increased ASD risk after controlling for maternal allergy, asthma, autoimmune conditions, gestational diabetes, hypertension, age, education, race/ethnicity, child conception year, conception season, sex, and gestational age. However, adjusting for the multiplicity of

hypotheses tested suggests that the results could be due to chance. If influenza vaccination during the first trimester of pregnancy causes ASD, our results suggest that it would amount to 4 additional ASD cases for every 1000 women vaccinated. Our finding of a possible association between maternal influenza vaccination in the first trimester and increased ASD risk parallels previous studies reporting an association between maternal viral infection^{7,9} or fever and increased ASD risk¹³ in the first trimester.

Although vaccination induces an inflammatory response during pregnancy, the magnitude and the duration of response is much lower and shorter, respectively, for influenza vaccination than viral infection.²⁷ Like infection, influenza vaccination during pregnancy has been reported to induce a transient increase in the levels of a number of proinflammatory cytokines, including interleukin 6, tumor necrosis factor α , and C-reactive protein.²⁷⁻³⁰ Studies on mice found an association between high interleukin-6 levels during pregnancy and abnormal behavior and brain structure.¹⁹ However, in epidemiological studies, associations between maternal cytokine levels and ASD have been mixed. While an earlier study³¹ found an association between elevated levels of C-reactive protein in the second trimester and increased ASD risk, a recent study³² did not find an association between maternal C-reactive protein and increased risk of ASD after controlling for maternal BMI. Elevated levels of interleukin 6 during pregnancy have been associated with increased risk of developmental delays but not ASD in one study³³ and with increased ASD risk with intellectual disability in another.³⁴

Table 2. Study Population Characteristics by Child Outcome, Kaiser Permanente Northern California Births (2000-2010)

Characteristic	Children, No. (%)		P Value
	With ASD (n = 3103)	Without ASD (n = 193 826)	
Sex			
Male	2545 (82.0)	98 242 (50.7)	<.001
Female	558 (18.0)	95 584 (49.3)	
Maternal age, mean (SD), y	31.64 (5.48)	30.63 (5.51)	<.001
Maternal education			
≤High school	675 (21.8)	53 877 (27.8.)	<.001
Some college	929 (29.9)	55 134 (28.5)	
College graduate	825 (26.6)	47 047 (24.3)	
Postgraduate	601 (19.4)	33 474 (17.3)	
Unknown	73 (2.4)	4294 (2.2)	
Maternal race/ethnicity			
White	1976 (63.7)	126 426 (65.2)	.03
Black	231 (7.4)	13 559 (7.0)	
Asian	797 (25.7)	46 490 (24.0)	
Other	99 (3.2)	7351 (3.8)	
Gestational age, wk			
<37	293 (9.4)	12 544 (6.4)	<.001
≥37	2810 (90.6)	181 282 (93.6)	
Maternal BMI before pregnancy, mean (SD)	27.32 (6.07)	26.67 (5.54)	<.001
Gestational diabetes	343 (11.0)	16 420 (8.5)	<.001
Maternal medical history before pregnancy			
Asthma	60 (1.9)	2474 (1.3)	.001
Autoimmune disease	64 (2.1)	3700 (1.9)	.54
Allergy	143 (4.6)	7624 (3.9)	.055
Hypertension	36 (1.2)	1348 (0.7)	<.002

Abbreviations: ASD, autism spectrum disorders; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

Table 3. Influenza Diagnosis, Influenza Vaccination During Pregnancy, and Risk of ASD: Kaiser Permanente Northern California Births, 2000-2010

Variable	Exposure Period				Unexposed During Pregnancy
	Anytime During Pregnancy	Trimesters			
		1st	2nd	3rd	
Diagnosis					
Total No.	1400	443	431	541	195 529
ASD cases, No. (%)	22 (1.57)	8 (1.81)	7 (1.62)	7 (1.29)	3081 (1.60)
Crude hazard ratio (95% CI)	1.00 (0.66-1.53)	1.16 (0.58-2.31)	1.05 (0.50-2.21)	0.81 (0.39-1.70)	1 [Reference]
Adjusted hazard ratio (95% CI) ^a	1.04 (0.68-1.58)	1.18 (0.59-2.37)	1.07 (0.51-2.25)	0.86 (0.41-1.80)	1 [Reference]
Crude risk difference	NE	NE	NE	NE	1 [Reference]
Vaccination					
Total No.	45 231	13 477	17 475	16 095	151 698
ASD cases, No. (%)	765 (1.69)	258 (1.91)	279 (1.60)	260 (1.62)	2338 (1.54)
Crude hazard ratio (95% CI)	1.11 (1.01-1.21)	1.26 (1.10-1.45)	1.03 (0.91-1.18)	1.02 (0.90-1.17)	1 [Reference]
Adjusted hazard ratio (95% CI) ^a	1.10 (1.00-1.21)	1.20 (1.04-1.39)	1.03 (0.90-1.19)	1.03 (0.90-1.20)	1 [Reference]
Crude risk difference	NE	0.40 (0.14-0.63)	NE	NE	1 [Reference]

Abbreviations: ASD, autism spectrum disorder; NE, not estimated.

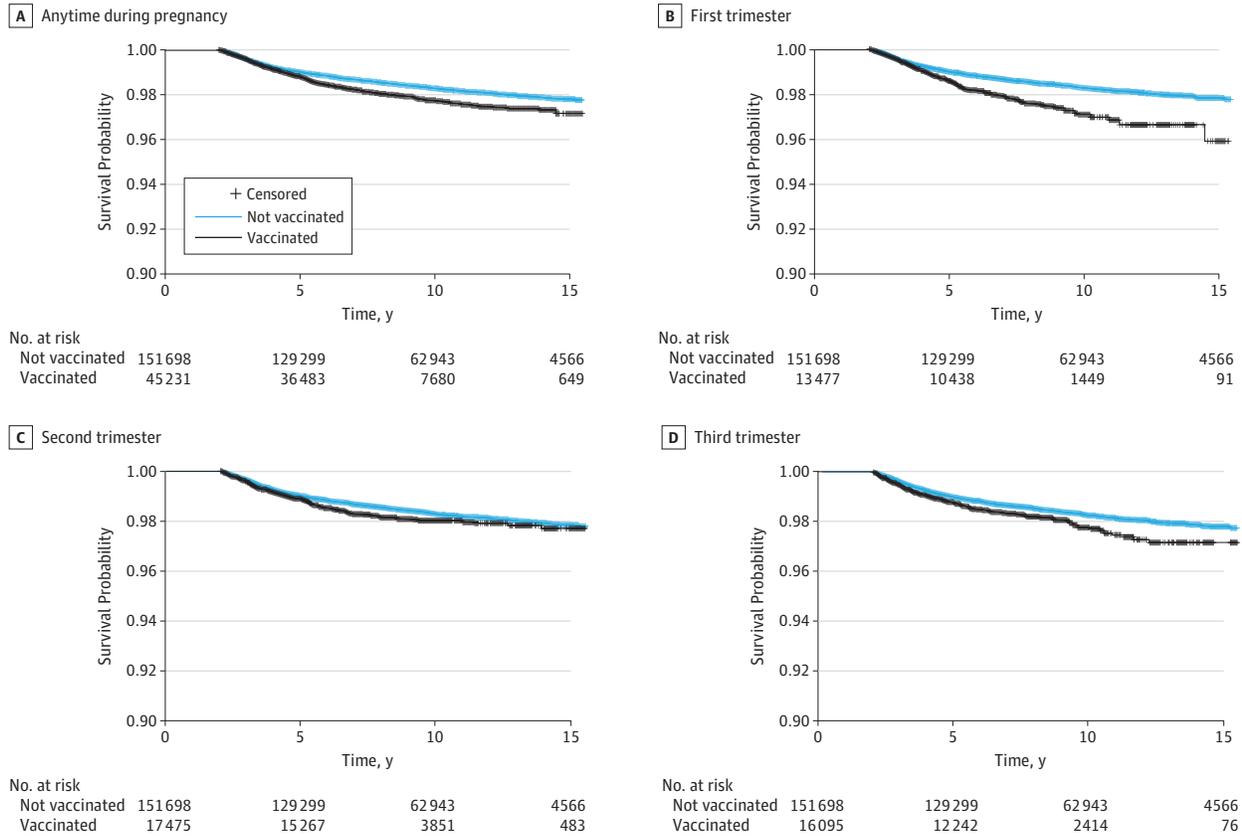
^a Hazard ratio adjusted for maternal allergy, asthma, autoimmune conditions, gestational diabetes, hypertension, age, education, race/ethnicity, child conception year, conception season, sex, and gestational age.

Limitations

Our findings have several study limitations. Autism spectrum disorder status was determined by diagnoses recorded in medical records and not validated by a standardized clinical assessment for all cases. However, when 50 children were evaluated with the Autism Diagnostic Interview-

Revised ³⁵ and the Autism Diagnostic Observation Schedule-Generic,³⁶ 94% met criteria for ASD on both instruments, and 100% met criteria on at least 1 instrument.³⁷ Record-review validation studies conducted by the investigators demonstrate that the predictors of valid ASD diagnoses were having more than 2 diagnoses in the

Figure. Kaplan-Meier Plots of Time From Birth to an Autism Spectrum Disorder Diagnosis in Children of Vaccinated Women Compared With Children of Unvaccinated Women



Product-limit survival estimates with numbers of participants at risk for anytime during the pregnancy (A), the first trimester (B), the second trimester (C), and the third trimester (D) for the periods from birth date until autism spectrum

order diagnosis, from birth date to leaving the health plan, or from birth date to the end of the study.

medical record.³⁸ Most influenza infections in our study were determined from *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnostic codes rather than serologic evidence. We were not able to review medical records to verify the influenza cases defined by the *International Classification of Diseases, Ninth Revision, Clinical Modification* codes. We also did not count subclinical infections or illnesses for which women did not seek medical attention. We did not have records for women who received their influenza vaccination outside KPNC facilities. However, previous studies found that more than 89% of KPNC members receive their seasonal influenza vaccination at KPNC facilities.³⁹ Although we controlled for major confounding factors related to influenza infection and vaccination and ASD, our results could result from unmeasured confounding factors that may be unknown or that we could not fully measure. Although the study had a large sample size, the number of exposed ASD cases was not large enough to provide a stable statistical estimate of the trimester-specific HR associated with influenza infection. Finally, our findings may be due to chance because the results were statistically insignificant after correcting for multiple comparisons.

Our study has several strengths despite the limitations, including population-based identification of cases from a large birth cohort and the use of prospectively collected information on influenza infection and vaccination documented in medical records. We were also able to examine risk associated with specific periods during pregnancy and to adjust for several important covariates.

Conclusions

We found no association between ASD risk and influenza infection during pregnancy or influenza vaccination during the second to third trimester of pregnancy. However, there was a suggestion of increased ASD risk among children whose mothers received influenza vaccinations early in pregnancy, although the association was insignificant after statistical correction for multiple comparisons. While we do not advocate changes in vaccine policy or practice, we believe that additional studies are warranted to further evaluate any potential associations between first-trimester maternal influenza vaccination and autism.

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