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Association between maternal influenza vaccination and neurodevelopmental disorders in childhood: a longitudinal, population-based linked cohort study

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ABSTRACT

Objective To assess the association between *in utero* exposure to seasonal inactivated influenza vaccine (IIV) and the risk of a diagnosis of a neurodevelopmental disorder in early childhood.

Design Retrospective cohort study.

Setting Population-based birth registry linked with health administrative databases in Western Australia (WA).

Participants Singleton, liveborn children born between 1 April 2012 and 1 July 2016 in WA.

Exposure Receipt of seasonal IIV during pregnancy obtained from a state-wide antenatal vaccination database.

Main outcome measures Clinical diagnosis of a neurodevelopmental disorder was recorded from hospital inpatient and emergency department records. We used Cox proportional hazard regression, weighted by the inverse-probability of treatment (vaccination), to estimate the hazard ratio (HR) of neurodevelopmental disorders associated with *in utero* exposure to seasonal IIV.

Results The study included 140 514 children of whom, 15 663 (11.2%) were exposed to seasonal IIV *in utero*. The prevalence of neurodevelopmental disorders was 5.4%, including mental or behavioural (0.4%), neurological (5.1%), seizure (2.2%) and sleep disorders (2.7%). Maternal IIV was not associated with increased risk of neurodevelopmental disorders (HR 1.00; 95% CI 0.91 to 1.08). Children exposed in the first trimester had a lower risk of seizure disorders (adjusted HR [aHR] 0.73; 95% CI 0.54 to 0.998), and preterm children exposed any time during pregnancy had a lower risk of sleep disorders (aHR 0.63; 95% CI 0.41 to 0.98).

Conclusions We did not observe increased risk of neurodevelopmental disorders following *in utero* exposure to seasonal IIV. Although we observed some evidence for lower risk of seizure and sleep disorders, additional studies are required to confirm.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Vaccine safety is a commonly cited reason for vaccine hesitancy and low uptake of influenza vaccines among pregnant people.
⇒ Few studies have evaluated the effect of maternal influenza vaccination on long-term paediatric health outcomes, including neurodevelopmental disorders in children exposed to influenza vaccines *in utero*.

WHAT THIS STUDY ADDS

⇒ Findings indicate no increase in the risk of neurodevelopmental disorders in early childhood associated with seasonal influenza vaccination during pregnancy.
⇒ While we identified a lower risk of seizure disorders when the vaccine was administered early in pregnancy and a lower risk of sleep disorders among preterm children of vaccinated mothers, additional investigation is warranted.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These results are supportive of the safety of prenatal administration of seasonal inactivated influenza vaccine and the continued provision of existing maternal vaccination programmes and policies.
⇒ This study may be useful in health practice for healthcare providers when providing vaccine counselling to pregnant people and prospective parents.

INTRODUCTION

Influenza causes serious morbidity and mortality through seasonal epidemics each year. Although seasonal inactivated influenza vaccine (IIV) is the most effective preventative tool to protect against influenza illness,[1] there are no current vaccines licensed for use for infants aged <6 months.[2] To protect mothers and their infants from infection, prenatal administration of seasonal IIV is recommended for pregnant people in many countries, including Australia, any stage during pregnancy.[2]

Considerable evidence supports the safety of maternal influenza vaccination in regard to adverse health outcomes at birth, including preterm birth, small-for-gestational age, spontaneous abortion, stillbirth, low birth weight, congenital malformations, and fetal death.[3–7] However, studies evaluating health outcomes following *in utero* exposure to seasonal IIV beyond early infancy are relatively scarce.[8] The Developmental Origins of Health and Disease hypothesis postulates that the prenatal period is a critical period of development and is susceptible to exposure to adverse agents, including infection, which can lead to long-term impacts on the health trajectory of children (ie, developmental programming).[9] Studies evaluating childhood health following *in utero* exposure to recommended vaccines are therefore needed.

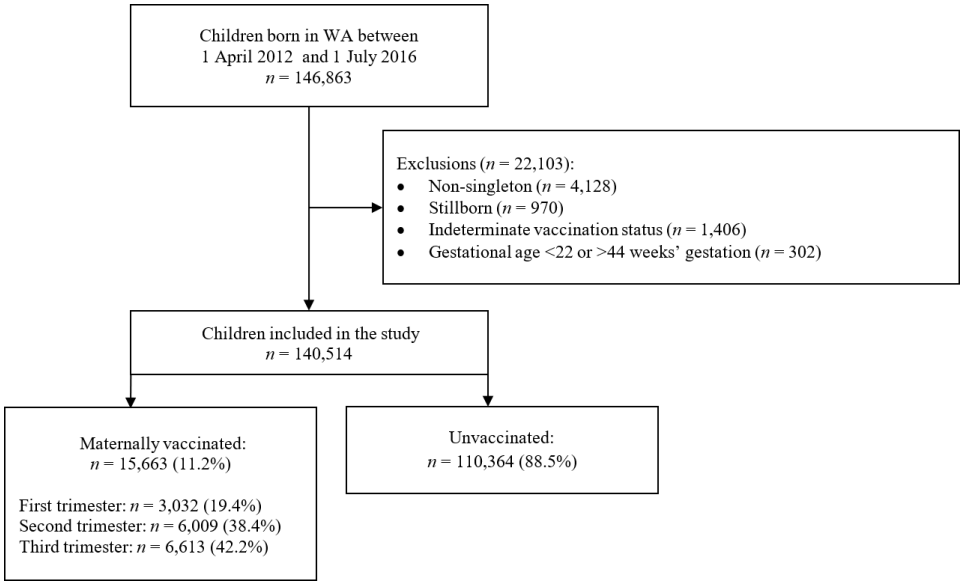

Figure 1 Flow diagram of study participants included in the cohort. WA, Western Australia.

We aimed to evaluate the association between seasonal IIV during pregnancy and paediatric neurodevelopmental health outcomes.

METHODS

Study cohort and design

This retrospective, population-based cohort study included all singleton, liveborn children born in Western Australia (WA) between 1 April 2012 and 1 July 2016 and their mothers (figure 1), identified using birth registrations. Mother-child pairs were probabilistically linked with other population-based administrative health datasets, including the Midwives Notification System (MNS), WA Antenatal Vaccination Database (WAAVD), Hospital Morbidity Data Collection, Emergency Department Data Collection, and death registrations (online supplemental table S1).[10] This study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline (STROBE checklist).

Maternal influenza vaccination

Information on influenza vaccination during pregnancy and date of vaccination were obtained from the WAAVD, a state-wide antenatal vaccine database managed by the WA Department of Health. Children of mothers who had received seasonal IIV during pregnancy were considered 'maternally vaccinated'. We calculated gestational age at vaccination from estimated date of conception to date of vaccination, using the best clinical estimate of gestational age and date of birth from the MNS. We excluded children of mothers who received seasonal IIV <2 weeks prior to birth (ie, 'indeterminate' vaccination status).[11]

Outcomes

Outcomes were identified from hospital inpatient and emergency department records.[12 13] We assessed the diagnosis of any neurodevelopmental disorder. Within these, we evaluated the diagnosis of mental or behavioural disorders and neurological disorders, as identified by diagnostic codes (ie, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification) in primary or additional diagnosis fields (online supplemental table S2). Within neurological disorders, we had sufficient data to separately evaluate seizure disorders, including epilepsy, and sleep disorders as health outcomes. We included presentations for all-cause injuries as a negative control outcome, to identify potentially biased non-causal associations between prenatal exposure to seasonal IIV and the outcomes—typically the result of uncontrolled confounding.[14]

Covariates

Maternal characteristics included age at delivery (continuous), Aboriginal and/or Torres Strait Islander status (hereafter respectfully referred to as Aboriginal), socioeconomic status,[15] body mass index (continuous), parity, pre-existing medical conditions, pregnancy complications, smoking during pregnancy, trimester at the first prenatal care visit and year and season of the pregnancy (measured from the date of delivery).

Missing data

For children with missing covariate information (n=16 652; 11.3%), we used multiple imputation by chained equations with 20 generated datasets to impute the missing data.

Statistical analyses

We compared the demographic and health characteristics between vaccinated and unvaccinated mothers and their children using univariate logistic regression models. Based on the predicted probability of vaccination from multivariate logistic regression, we estimated the inverse-probability of treatment (vaccination) weights (IPTW) to control for baseline probability of vaccination. To account for lack of independence for children with the same mother, we included the mother as a cluster variable. The final IPTW model included maternal age, body mass index, Aboriginal status, trimester of the first prenatal care visit, smoking during pregnancy, socioeconomic status, pre-existing medical conditions, pregnancy complications, and the year and season of birth. Because the pregnancy complications included in our study were predominantly diagnosed at 24 weeks of pregnancy,[16 17] to appropriately account for temporality, pregnant people who were vaccinated before 24 weeks' gestation were considered to not have influenced a pregnant person's decision

to vaccinate. We did not include pregnancy complications as a covariate in IPTW models for first trimester vaccination. IPTWs were trimmed at the 1st and 99th percentile. To assess the balance of maternal covariates included in the multivariate model, we examined the standardised mean differences of each covariate for maternally vaccinated and unvaccinated children. IPTWs were applied to trimmed and weighted Cox proportional hazards regression models to estimate HRs with 95% CIs for each study outcome.

Children were followed from the date of birth and were censored at the earliest of the: (a) date the child reached 5 years of age, (b) last date of available data (30 June 2017), (c) date the child died or (d) date of the event. To evaluate associations with more severe clinical outcomes, additional analyses defined outcomes based on hospital admission data only. To evaluate the importance of timing of maternal vaccination and duration of exposure to maternal antibodies, stratified analyses were planned *a priori* and performed by (1) trimester of vaccination, and by (2) preterm birth status, to determine whether results differed by length of gestation. All analyses were performed in Stata V.15.1 (StataCorp, USA). Post hoc power analysis was computed to determine the detectable difference in the risk of the outcome measures, with 90% and 80% power and alpha of 5%, between maternally vaccinated and unvaccinated children (online supplemental table S3).

RESULTS

A total of 146 863 children born in WA were identified; 6349 (4.3%) children were excluded because the child was a non-singleton (n=4128), stillborn (n=970), and/or had indeterminate vaccination status (n=1406); 140 514 singleton, liveborn children from 117 359 mothers were included in the study (figure 1).

Among the 140 514 children, 15 663 (11.2%) were maternally vaccinated: 3034 (19.4%) during the first trimester, 6014 (38.4%) during the second trimester, 6615 (42.2%) during the third trimester. Vaccination was more common among primiparous pregnant people and pregnant people with pre-existing medical conditions, and pregnant people who gave birth during winter compared with summer (table 1). Pregnant people who were of the lowest socioeconomic status, overweight, smoked during pregnancy, received no or later prenatal care and mothers of preterm infants were less likely to be vaccinated. After trimming and weighting, maternal characteristics were balanced (<10% difference) between maternally vaccinated and unvaccinated children (online supplemental figure S1) and the predicted probability of vaccination was similar with no extreme weights (online supplemental figure S2).

We identified 7436 (5.3%) children with a diagnosis of a neurodevelopmental disorder. We observed no association between risk of neurodevelopmental disorders and maternal influenza vaccination (adjusted HR [aHR] 1.00; 95% CI 0.91 to 1.08) (table 2) nor after stratifying by trimester of vaccination (table 2), preterm birth status (online supplemental tables S4 and S5) or when restricting to hospital admissions (online supplemental table S6).

There were 505 (0.4%) children with a diagnosis of a mental or behavioural disorder. The most common outcomes included disorders of psychological development (n=206; 40.8%) and behavioural and emotional disorders (n=121; 24.0%). There was no association between risk of mental or behavioural disorders and maternal influenza vaccination (aHR 0.97; 95% CI 0.70 to 1.35) (table 2) nor after stratifying by trimester of vaccination

Table 1 Odds of seasonal influenza vaccination by maternal and child characteristics for children born in Western Australia between 1 April 2012 and 1 July 2016

Characteristic	Maternally unvaccinated (n=124 851) n (%)	Maternally vaccinated (n=15 663) n (%)	OR (95% CI)
Maternal characteristics			
Age (years)			1.01 (1.00 to 1.01)
≤19	3942 (3.2)	501 (3.2)	**1.12 (1.01 to 1.25)**
20–24	17 188 (13.8)	1947 (12.4)	Reference
25–29	35 774 (28.7)	4329 (27.6)	**1.07 (1.01 to 1.13)**
30–34	42 177 (33.8)	5573 (35.6)	**1.17 (1.10 to 1.23)**
≥35	25 770 (20.6)	3313 (21.2)	**1.13 (1.07 to 1.20)**
Aboriginal status			
Aboriginal	6503 (5.2)	832 (5.3)	1.02 (0.95 to 1.10)
Non-Aboriginal	118 348 (94.8)	14 831 (94.7)	Reference
Socioeconomic status*			
Quintile 1 (most disadvantaged)	24 965 (20.0)	2925 (18.7)	**0.89 (0.85 to 0.94)**
Quintile 2	25 681 (20.6)	3277 (20.9)	0.97 (0.92 to 1.03)
Quintile 3	26 558 (21.3)	3248 (20.7)	**0.93 (0.89 to 0.98)**
Quintile 4	24 787 (19.9)	3219 (20.6)	0.99 (0.94 to 1.05)
Quintile 5 (least disadvantaged)	22 860 (18.3)	2994 (19.1)	Reference
Body mass index			1.00 (1.00 to 1.00)
<18.5 (underweight)	4243 (3.4)	501 (3.2)	0.92 (0.84 to 1.01)
18.5 to <25 (normal)	59 174 (47.4)	7582 (48.4)	Reference
25 to <30 (overweight)	35 544 (28.5)	4302 (27.5)	**0.94 (0.91 to 0.98)**
≥30 (obese)	25 890 (20.7)	3278 (20.9)	0.99 (0.95 to 1.03)
Parity			
Primiparous	53 244 (42.7)	7335 (46.8)	Reference
1 prior birth	43 296 (34.7)	5405 (34.5)	**0.91 (0.87 to 0.94)**
≥2 prior births	28 311 (22.7)	2923 (18.7)	**0.75 (0.72 to 0.78)**
Pre-existing medical conditions			
Asthma†	12 859 (10.3)	1731 (11.1)	**1.08 (1.03 to 1.14)**
Essential hypertension†	1623 (1.3)	282 (1.8)	**1.39 (1.23 to 1.58)**
Pre-existing diabetes mellitus†	1044 (0.8)	202 (1.3)	**1.55 (1.33 to 1.80)**
Pregnancy complications			
Gestational diabetes†	12 487 (10.0)	969 (6.2)	**0.59 (0.55 to 0.63)**
Gestational hypertension†	5719 (4.6)	464 (3.0)	**0.64 (0.58 to 0.70)**
Pre-eclampsia†	4107 (3.3)	319 (2.0)	**0.61 (0.54 to 0.69)**
Smoked during pregnancy	12 549 (10.1)	1403 (9.0)	**0.88 (0.83 to 0.93)**
Trimester at the first prenatal care visit			
First trimester	82 329 (65.9)	11 131 (71.1)	Reference
Second trimester	36 161 (29.0)	4075 (26.0)	**0.83 (0.80 to 0.87)**
Third trimester	6130 (4.9)	449 (2.9)	**0.54 (0.49 to 0.60)**
No prenatal care	231 (0.2)	8 (0.1)	**0.26 (0.13 to 0.52)**
Year of birth			
2012	22 844 (18.3)	1400 (8.9)	Reference
2013	29 458 (23.6)	3165 (20.2)	**1.75 (1.64 to 1.87)**
2014	29 827 (23.9)	3513 (22.4)	**1.92 (1.80 to 2.05)**
2015	27 444 (22.0)	5558 (35.5)	**3.30 (3.11 to 3.51)**

Continued

Table 1 Continued

Characteristic	Maternally unvaccinated (n=124 851) n (%)	Maternally vaccinated (n=15 663) n (%)	OR (95% CI)
2016	15 278 (12.2)	2027 (12.9)	**2.16 (2.02 to 2.32)**
Season of birth			
Summer (December–February)	30 700 (24.6)	2382 (15.2)	Reference
Autumn (March–May)	36 337 (29.1)	2524 (16.1)	**0.90 (0.84 to 0.95)**
Winter (June–August)	29 431 (23.6)	5893 (37.6)	**2.58 (2.45 to 2.71)**
Spring (September–November)	28 383 (22.7)	4864 (31.1)	**2.21 (2.10 to 2.33)**
Child characteristics			
Sex‡			
Male	64 244 (51.5)	8005 (51.1)	Reference
Female	60 604 (48.5)	7658 (48.9)	1.01 (0.98 to 1.05)
Aboriginal status			
Aboriginal	7043 (5.6)	915 (5.8)	1.04 (0.97 to 1.11)
Non-Aboriginal	117 808 (94.4)	14 748 (94.2)	Reference
Birth outcomes			
Preterm birth	8576 (6.9)	980 (6.3)	**0.90 (0.85 to 0.97)**
Moderate-to-late preterm	7572 (6.1)	908 (5.8)	0.95 (0.88 to 1.02)
Very preterm	644 (0.5)	54 (0.3)	**0.66 (0.50 to 0.88)**
Extremely preterm	360 (0.3)	18 (0.1)	**0.40 (0.25 to 0.64)**
Small-for-gestational age§	10 202 (8.2)	1304 (8.3)	1.02 (0.96 to 1.08)

Bold values indicate statistically significant associations.

*Socioeconomic status was based on the Socioeconomic Index for Areas Index of Relative Socioeconomic Advantage and Disadvantage, an area-based index of relative access to resources for households within the same census collection district.[15]
†Comparisons were between the presence and absence of the condition by treatment groups.
‡The sex of <5 maternally unvaccinated children was unknown.
§Small-for-gestational age was based on the Australian national birth weight percentiles by sex and gestational age.[31]

(table 2), preterm birth status (online supplemental tables S4 and S5) or when restricting to hospital admissions (online supplemental table S6).

In total, there were 7093 (5.0%) children diagnosed with a neurological disorder. The most common outcome included episodic and paroxysmal disorders (n=3880; 54.7%); 3055 (43.1%) episodes for a seizure disorder and 3696 (52.1%) for a sleep disorder. No associations were observed between risk of neurological disorders and maternal influenza vaccination (aHR 1.00; 95% CI 0.91 to 1.09) (table 2). Similarly, we observed no associations when stratifying by trimester of vaccination (table 2), preterm birth status (online supplemental tables S4 and S5) or when restricting to hospital admissions (online supplemental table S6).

Of children diagnosed with a seizure disorder, 354 (11.6%) diagnoses were epilepsy or status epileptus and 2709 (88.7%) were convulsions. We observed no association between risk of seizure disorders and maternal influenza vaccination (aHR 0.99; 95% CI 0.87 to 1.14). When stratifying by trimester, we observed a lower risk of seizure disorders following vaccination during the first trimester (aHR 0.73; 95% CI 0.54 to 0.998) (table 2). This association was only observed among term children vaccinated during the first trimester (aHR 0.72; 95% CI 0.52 to 0.999) (online supplemental table S4). No other associations were observed following vaccination during later trimesters (table 2), when stratifying by preterm birth status (online supplemental tables S4 and S5) or when restricting to hospital admissions (online supplemental table S6).

Among children diagnosed with a sleep disorder, 3557 (96.2%) diagnoses were sleep apnoea. There was no association between sleep disorders and maternal influenza vaccination (aHR 0.97; 95% CI 0.85 to 1.10) (table 2). When stratifying by preterm birth status, we observed a lower risk of sleep disorders among preterm children of vaccinated mothers (aHR 0.63; 95% CI 0.41 to 0.98) (online supplemental table S5). There were no other associations when stratifying by trimester of vaccination (table 2), preterm birth status (online supplemental tables S4 and S5) or when restricting to hospital admissions (online supplemental table S6). There was no association between risk of all-cause injuries and maternal influenza vaccination overall (aHR 1.04; 95% CI 0.99 to 1.09) (online supplemental table S7) or when stratifying by trimester of vaccination (online supplemental table S7).

DISCUSSION

In this large, population-based cohort study of 140 514 children, we found no evidence of an increased risk of neurodevelopmental disorders among children aged <5 years following prenatal exposure to seasonal IIV. However, we did observe an indication of a lower risk of seizure disorders following seasonal IIV administered during the first trimester and sleep disorders among preterm children of vaccinated mothers. These results support the safety of maternal influenza vaccination and continuance of existing maternal vaccination programmes and policies.

To date, most studies evaluating maternal influenza vaccination have focused on outcomes in the first 6 months of life.[3] To our knowledge, only three studies have assessed neurodevelopmental outcomes among children >6 months of age, two examining pandemic vaccines and one examining seasonal IIV.[18–20] These studies identified no association between maternal influenza vaccination and paediatric neurodevelopmental disorder development. Zerbo *et al*[20] observed a suggestion of increased risk of autism spectrum disorder (ASD) following prenatal exposure to seasonal IIV in the first trimester (aHR 1.20; 95% CI 1.04 to 1.39). However, accounting for multiple comparisons using Bonferroni-corrected CIs, this association was no longer significant (p=0.1). We identified 22 children with a diagnosis for ASD; due to an insufficient number of cases among the vaccinated cohort (n<5), the analysis of ASD was not possible. Hviid *et al*[19] reported no association between epilepsy among children exposed to pandemic influenza vaccine in the first trimester (adjusted risk ratio [aRR] 1.01; 95% CI 0.21 to 4.74) nor in the second or third trimester (aRR 1.22; 95% CI 0.79 to 1.86).

Our results examining composite outcomes and seizure disorders mostly align with previous studies examining individual outcomes. We observed a decreased risk of seizure disorders following first trimester influenza vaccination. To our knowledge, there have been no previous studies evaluating the association between maternal influenza vaccination and paediatric sleep disorders, and this novel finding requires additional investigation. While we cannot entirely rule out the possible influences of bias and type I error in the results from this observational

Table 2 Risk of neurodevelopmental disorders associated with prenatal exposure to seasonal inactivated influenza vaccine among children <5 years of age, by trimester of prenatal vaccination

	Unexposed to seasonal influenza vaccine during pregnancy (n=124 851) (n=122 385)*	Exposed to seasonal influenza vaccine during pregnancy (n=15 663) (n=15 272)*	Trimester of vaccine exposure		
			First trimester (n=3034) (n=2959)*	Second trimester (n=6014) (n=5896)*	Third trimester (n=6615) (n=6417)*
Neurodevelopmental disorder					
Cases, n (%)	6710 (5.4)	726 (4.6)	143 (4.7)	304 (5.1)	279 (4.2)
Unweighted HR (95% CI)	1 (reference)	1.01 (0.94 to 1.09)	1.02 (0.87 to 1.21)	1.03 (0.92 to 1.15)	0.99 (0.88 to 1.12)
Cases, n (%)	6594 (5.4)	713 (4.7)	140 (4.7)	299 (5.1)	274 (4.3)
Weighted HR (95% CI)†	1 (reference)	1.00 (0.91 to 1.08)	0.99 (0.82 to 1.18)	1.04 (0.91 to 1.18)	0.95 (0.83 to 1.09)
Mental or behavioural disorder					
Cases, n (%)	456 (0.4)	49 (0.3)	7 (0.2)	24 (0.4)	18 (0.3)
Unweighted HR (95% CI)	1 (reference)	1.02 (0.76 to 1.37)	0.75 (0.36 to 1.58)	1.21 (0.80 to 1.83)	0.95 (0.59 to 1.52)
Cases, n (%)	447 (0.4)	47 (0.3)	6 (0.2)	24 (0.4)	17 (0.3)
Weighted HR (95% CI)†	1 (reference)	0.97 (0.70 to 1.35)	0.69 (0.29 to 1.63)	1.19 (0.75 to 1.88)	0.91 (0.54 to 1.54)
Neurological disorder					
Cases, n (%)	6399 (5.1)	694 (4.4)	139 (4.6)	290 (4.8)	265 (4.0)
Unweighted HR (95% CI)	1 (reference)	1.02 (0.94 to 1.10)	1.04 (0.88 to 1.24)	1.03 (0.92 to 1.16)	0.99 (0.88 to 1.12)
Cases, n (%)	6291 (5.1)	683 (4.5)	137 (4.6)	285 (4.8)	261 (4.1)
Weighted HR (95% CI)†	1 (reference)	1.00 (0.91 to 1.09)	1.00 (0.83 to 1.20)	1.04 (0.91 to 1.19)	0.95 (0.83 to 1.10)
Seizure disorder					
Cases, n (%)	2744 (2.2)	311 (2.0)	52 (1.7)	132 (2.2)	127 (1.9)
Unweighted HR (95% CI)	1 (reference)	0.99 (0.88 to 1.11)	0.84 (0.64 to 1.11)	1.03 (0.87 to 1.23)	1.01 (0.85 to 1.21)
Cases, n (%)	2695 (2.2)	303 (2.0)	50 (1.7)	127 (2.2)	126 (2.0)
Weighted HR (95% CI)†	1 (reference)	0.99 (0.87 to 1.14)	**0.73 (0.54 to 0.998)**	1.10 (0.90 to 1.35)	1.00 (0.81 to 1.22)
Sleep disorder					
Cases, n (%)	3369 (2.7)	327 (2.1)	72 (2.4)	134 (2.2)	121 (1.8)
Unweighted HR (95% CI)	1 (reference)	0.98 (0.88 to 1.11)	1.12 (0.89 to 1.42)	0.96 (0.81 to 1.14)	0.96 (0.80 to 1.15)
Cases, n (%)	3317 (2.7)	325 (2.1)	72 (2.4)	134 (2.3)	119 (1.9)
Weighted HR (95% CI)	1 (reference)	0.97 (0.85 to 1.10)	1.11 (0.86 to 1.42)	0.96 (0.80 to 1.16)	0.91 (0.74 to 1.11)

Bold values indicate statistically significant associations.
All outcomes were identified from ICD-10-AM codes found in the principal and 20 additional diagnosis fields of hospital inpatient and emergency department presentation records, and from the presenting symptom code found in the emergency department presentation records (online supplemental table 2).
*Sample size after trimming the 1st and 99th percentile of the predicted probability of vaccination.
†HRs were weighted by trimmed inverse-probability of treatment weights factoring for maternal covariates including age, Aboriginal status, socioeconomic status, body mass index, parity, pre-existing medical conditions (asthma, essential hypertension, pre-existing diabetes), pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia), smoking status during pregnancy, trimester at the first prenatal care visit, year and season of birth.
ICD-10-AM, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification.

study, several aspects of our study suggest a plausible protective relationship between maternal immunisation and the subsequent development of neurodevelopmental conditions in offspring.

Previous studies have observed adverse neurodevelopmental outcomes, including ASD, following prenatal exposure to viral or bacterial infections in offspring, including influenza infection.[9] Influenza infection and subsequent maternal immune activation during pregnancy has been implicated in the development of seizure disorders in offspring.[21 22] Using data from Norway, Canada and Australia, Oakley *et al*[23] identified a higher risk of seizure disorders (aHR 1.17; 95% CI 1.07 to 1.28) and febrile seizures (aHR 1.20; 95% CI 1.07 to 1.34) following maternal influenza infection. Vaccination during pregnancy is effective in preventing maternal influenza infection. A meta-analysis of 19 studies from 11 countries identified a lower incidence of laboratory-confirmed influenza among pregnant people following exposure to seasonal IIV during pregnancy (vaccine effectiveness, 63%).[24] Protection against influenza virus infection through maternal immunisation could therefore result in the reduced risk of influenza infection during pregnancy, and as a result prevent neurological harm to the fetal brain.

The strengths of our study include the use of a large, population-based mother-infant cohort with detailed information on maternal sociodemographic and health characteristics, receipt of prenatal vaccine, and record linkage to several administrative health datasets permitting follow-up of outcomes up to 5 years. The record linkage system in WA is long-standing, with expertise in linking large administrative health data since 1995.[25] With the exception of the antenatal vaccination database, these datasets are legally mandated, and have high data quality.[26] The MNS is estimated to capture 99% of all births in WA.[27] Because observational studies are subject to uncontrolled confounding, we assessed this using negative control analysis, which is increasingly used in observational studies to detect uncontrolled confounding between treatment groups. After adjusting for measured confounders, any observed association between the exposure and the negative control outcome would suggest residual confounding which we did not observe. However, it is possible that the negative control outcome in our study may not detect all possible residual confounding.[28]

Despite these strengths, our study has limitations. First, these data are observational and we cannot rule out residual uncontrolled confounding and healthy vaccinee bias. Pregnant mothers with underlying chronic conditions are more likely to be vaccinated compared with their healthier counterparts.[29] However, we attempted to restrict the influence of health-seeking behaviour using IPTW. Second, maternal vaccination data linked from the WAAVD relied on immunisation reports from medical providers; although these records have high specificity, they are likely to be incomplete.[30] Third, outcomes were limited by diagnoses recorded in hospital inpatient and emergency department records, which do not capture outcomes diagnosed and treated in primary care. However, as severe medical events are unlikely to be managed entirely through primary care, especially in young children, we believe the majority of severe events are captured in our dataset. For this reason, our results may be more reflective of severe paediatric neurodevelopmental conditions. Finally, despite the large size of our cohort, small cell sizes (ie, <5) made it impractical to estimate effects by preterm birth status or when restricting to hospital admissions for all outcomes.

CONCLUSIONS

Our findings indicate seasonal IIV during pregnancy is not associated with adverse neurodevelopmental outcomes among children aged up to 5 years and support current global vaccine policies prioritising influenza immunisation for pregnant people. Our study detected a potential lower risk of seizure disorders following seasonal IIV administered in the first trimester and sleep disorders among preterm children of vaccinated mothers, these findings warrant further investigation. This information may be useful to reassure pregnant people and inform their healthcare providers when making vaccine decisions and providing vaccine counselling.

Correction notice This article has been amended since it was first published. Figure 1 has been replaced with the correct version.

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Contributors DF conceptualised the study, contributed to the methodology, performed the formal analysis, drafted the initial manuscript and reviewed and revised the manuscript. DF is the guarantor and accepts full responsibility for the finished work, the conduct of the study, had access to the data, and controlled the decision to publish. GP, MS and HCM contributed to the methodology and critically reviewed the manuscript for important intellectual content during manuscript drafting and revision. AKR conceptualised the study, was responsible for funding acquisition, contributed to the methodology and critically reviewed the manuscript for important intellectual content during manuscript drafting and revision.

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