

Autism Spectrum Disorders in Children Exposed in Utero to Hyperemesis Gravidarum

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Abstract

Objective This study aimed to determine if hyperemesis gravidarum (HG) is associated with autism spectrum disorder (ASD) risk, and how this association is influenced by race, ethnicity, sex, exposure timing, and medication used to treat it.

Study Design This is a retrospective cohort study using records from 469,789 mother-child pairs who delivered at Kaiser Permanente Southern California (KPSC) hospital (1991–2014). Singleton-born children were followed longitudinally from 2 to 17 years of age. Clinical records were used to determine the diagnosis of HG and specialist-confirmed diagnosis of ASD.

Results Children exposed to HG in-utero had higher rates of ASD than unexposed children (2.87 vs. 1.71/1,000 person-years; adjusted hazard ratio [adj.HR]: 1.53; 95% confidence interval [CI]: 1.37–1.70). Children exposed at first and second trimester of pregnancies were more likely to develop ASD; 1.58-fold (95% CI: 1.40–1.79), and 1.36-fold (95% CI: 1.05–1.75), respectively, compared with unexposed children. HG was associated with ASD for boys (adj.HR: 1.50; 95% CI: 1.33–1.70) and girls (adj.HR: 1.62; 95% CI: 1.28–2.05). HG was significantly associated with ASD risk in white and Hispanic children. The medications used to treat HG did not contribute to ASD risk.

Conclusion HG diagnosis is associated with ASD risk and may be helpful in identifying at-risk children who could benefit from enhanced surveillance and earlier diagnosis and intervention.

Keywords

- ▶ autism
- ▶ neurodevelopment
- ▶ hyperemesis gravidarum
- ▶ race
- ▶ ethnicity

Autism spectrum disorder (ASD) affects 1 in 68 children in the United States¹ and its prevalence has dramatically increased over the last two decades.^{2,3} It persists into adulthood and is a significant burden to families and society.^{4,5} Although genetic

and environmental factors have been suggested, though no specific cause of the condition has been identified, and it is thought to be a complex disorder of the developing brain with multifactorial etiology affecting the brain at critical times

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during development. Potential risk factors include advanced parental age, white race, male sex, and multiple births.^{6–8} Antepartum and intrapartum conditions,^{9,10} preterm birth,¹¹ small for gestational age birth,¹² having a sibling with autism,^{13,14} and mood disorders in family members¹⁵ have also been suggested to increase risk.

Hyperemesis gravidarum (HG), a severe form of nausea and vomiting, affects 0.3 to 4% of pregnant women^{16–18} and can result in maternal weight loss, malnutrition, dehydration, and electrolyte/acid-base imbalance and low birth-weight and small-for-gestational age birth of infant morbidity.^{16,19} Like autism, its pathoetiology is unknown but risk factors include family history, HG in a prior pregnancy, non-white race, female fetus, multiple gestation, and low body mass index.^{16,20–23} Previous studies suggest that metabolic problems, such as undernutrition,^{24,25} gestational diabetes mellitus (GDM),⁹ and hypothyroidism²⁶ during early pregnancy may lead to neurodevelopmental conditions, such as schizophrenia and ASD. Therefore, we hypothesized that HG is associated with increased ASD risk in the children and that this association may be modified by child's sex, race/ethnicity, timing of first in utero exposure, severity of the condition, and gestational age at birth.

Materials and Methods

We conducted a retrospective longitudinal cohort study using medical records of pregnant women and their children ($n = 469,789$) born between January 1, 1991 and December 31, 2014 at all Kaiser Permanente Southern California (KPSC) hospital. To be eligible, children must have been born to KPSC-members, be a live-singleton birth between 28^{0/7} and 42^{6/7} weeks of gestation and be a KPSC health plan member for ≥ 3 months between 2 and 17 years of age. The study cohort composition is shown in **►Supplementary Appendix A: ►Supplementary Fig. S1** (available in the online version). Children's medical records were linked longitudinally to biological mothers using unique identifiers. The linked medical records contain information on maternal sociodemographic and behavioral characteristics, maternal medical and obstetrical history, and complete child health care information. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes from inpatient and outpatient physician encounters, as well as laboratory results and pharmacy records were used to ascertain the exposure and outcome of interest. Validation of the linked data have been reported in detail elsewhere.²⁷ Institutional review board approval was obtained for this study.

The primary exposure of interest was the clinical diagnosis of HG (ICD-9-CM code 643.0x and 643.1x). To assess the effect of the severity of illness on ASD risk, we chose an approach with indicators of a more severe form of the condition that likely requires hospitalization. This approach used the following diagnoses and procedures: HG with metabolic disturbance (ICD-9-CM codes 643.1x and 99.18), requiring nasogastric enteral feeding (ICD-9-CM codes 96.07, and current procedural terminology [CPT] codes 43752 and 43760), and total parenteral nutrition (ICD-9-CM codes 96.07, 96.08, 96.6, 99.15, and 99.18).

To ascertain a diagnosis of ASD, we used the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)²⁸ for any of the following conditions: autistic disorder, childhood disintegrative disorder, Rett's disorder, Asperger's disorder, or pervasive developmental disorder, not otherwise specified. Children, ages between 2 and 17 years, with at least one documented DSM-IV-TR code for ASD on any two separate visits during the follow-up period formed the ASD cases. Clinical experts validated the accuracy of these codes through medical record review.²⁹ As per KPSC guidelines, last revised April 2013,³⁰ ASD services are covered by a plan (a child/adolescent psychiatrist, developmental/behavioral pediatrician, child psychologist, or neurologist). The experts are required to perform a series of behavioral and developmental surveillance at all well-child visits, as early as 4 months of age. If there is a sufficient degree of suspicion, a modified version of the checklist for autism in toddlers [M-CHAT]³¹ and developmental screening questionnaires for toddlers is completed (as early as 18 months of life). For each diagnosed child, a treatment plan is developed and provided by a qualified provider in autism services.

Potential confounders/modifiers in this study include child's race/ethnicity and sex, maternal age (<25, 25–34, and ≥ 35 years), education (<12, 12, and ≥ 13 years), median family household income based on census tract of residence, timing of prenatal care initiation, smoking during pregnancy (yes/no), gestational age at delivery based on clinical estimates, and maternal comorbidities. Maternal and paternal race/ethnicity defined the child's race/ethnicity. A child was categorized non-Hispanic white (white) if born to non-Hispanic white mother and father. The same applies to non-Hispanic black (black), Hispanic, and Asian/Pacific Islander race/ethnicity groups. The Other/Multiple race/ethnicity category includes children born from interracial/interethnic relationship. The electronic medical and pharmacy records contain detailed clinical and drug-dispensing data on medications commonly used to treat mild form of HG (diphenhydramine, promethazine, ondansetron, and metoclopramide), nutritional interventions (nasogastric enteral feeding and total parenteral nutrition), and injection or infusion of electrolytes.

Follow-up of children started from the delivery date until the date of ASD diagnosis. Censoring occurred on the earliest of the following dates: health plan disenrollment, 17th birthday, non-ASD related death, or end of study (December 31, 2016). We examined the distributions of maternal and child characteristics by HG status using χ^2 tests. HG may recur between pregnancies and ASD also tends to recur in siblings; such clustered observations are likely to be correlated. Therefore, to examine the association between prenatal exposure to HG and ASD, we used marginal Cox's proportional hazards model to account for within-cluster correlation. Confounding variables were chosen a priori or if they resulted in p -value < 0.05.

Because the timing and severity of prenatal exposure, and the fact that child's sex and gestational age at birth may influence ASD risk, we stratified the data for these potential mediators (**►Table 3**, **►Supplementary Appendix B: ►Supplementary Fig. S2** [available in the online version]).

To assess the impact of the severity of illness on the association between prenatal exposure to HG and ASD, we compared the association of HG with metabolic disturbances to those without. We also examined the effect of HG treatments on the observed association for each level of disease-modifying therapy after limiting the analysis to pregnancies ($n = 190,126$) with complete medication data available during the study period (2006–2014). We performed the following sensitivity analyses (–**Supplementary Appendix C: –Supplementary Table S1** [available in the online version]) to evaluate the relative influence of each parameter on the observed risk relationships: (1) exclude children with only one ASD diagnosis, (2) exclude children with a history of congenital anomalies and developmental and emotional comorbidities (mental retardation, developmental dyslexia, deficits in language processing, conduct disorder, irritability, bipolar or anxiety disorders, and depression), (3) exclude pregnancies with a history of medical and/or perinatal adversities including gestational hypertension, diabetes, intrauterine growth restriction (IUGR), and low birth weight, (4) limit the cohort to children aged ≥ 4 years because children aged 2 to 3 years may have shorter follow-up period to capture events, (5) limit the cohort to children without genetic predisposition, (6) account for maternal comorbidities (–**Supplementary Table S2** [available in the online version]), (7) account for “year of birth,” (8) account for maternal prepregnancy body mass index (BMI, kg/m²) in the model, and (9) examine the potential effects of residual confounders on the observed association using a range of E-values for the overall result and the lower limits of their 95% confidence intervals (CI) observed in Cox’s regression models.³² The E-values were estimated using the online calculator for hazard ratios (HR) with an outcome prevalence of $<15\%$. Crude and adjusted HR and 95% CI were used to quantify the magnitude of associations. The analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

We identified 469,789 children, aged between 2 and 17 years, who were born singleton in all KPSC hospitals between January 1, 1991 and December 31, 2014 with at least 90 days active enrollment during the follow-up periods (1993–2016). During the study period, 8,447 (1.8%) children were diagnosed with ASD. The mean age at first diagnosis was 6 years (standard deviation [SD] = 3.3). The mean follow-up time was 10.4 years (SD = 4.7) for children diagnosed with ASD.

Compared with women without a history of HG, women with a history of HG were more likely to be 20 to 29 years of age, have completed ≥ 12 years of education, have a high-household income, be nulliparous, and not smoke during pregnancy (–**Table 1**). The rate of prenatal exposure to HG varied by child’s race/ethnicity and sex. Black and Asian/Pacific Islander children were more likely to be exposed to HG. Girls were more likely than boys to be exposed. Exposed children were more likely to be born preterm than unexposed children.

Compared with unexposed children (1.71/1,000 person-years), the overall ASD incidence rate in exposed children was higher (2.87/1,000 person-years; adjusted HR: 1.53; 95% CI:

1.37–1.70). This remained significant when HG diagnosis was made during the first (HR: 1.58; 95% CI: 1.40–1.79) and second (HR: 1.36; 95% CI: 1.05–1.75) trimesters of pregnancy (–**Table 2**). Exposure to HG was associated with ASD risk, regardless of the severity of the exposure. Limiting the cohort to children aged 4 to 17 years had no effect on our findings.

The association between prenatal exposure to HG and childhood ASD was modified by gestational age at birth (–**Table 3, –Supplementary Appendix B: –Supplementary Fig. S2** [available in the online version]). In term-born children, prenatal exposure to HG is associated with a 1.39-fold increased ASD risk (95% CI: 1.23–1.56), with the greatest risk occurring after exposure in the first (HR: 1.44; 95% CI: 1.26–1.64) and second (HR: 1.21; 95% CI: 0.91–1.61) trimesters, although the latter did not attain statistical significance. In preterm children, ASD incidence rates were twice as common in the exposed (4.82/1,000 person-years) compared with unexposed (2.27/1,000 person-years) groups, with significantly increased risk during the first (HR: 1.95; 95% CI: 1.35–2.72) and second (HR: 2.27; 95% CI: 1.28–4.02) trimesters. When further stratified by severity of fetal exposure, risk did not differ substantially at preterm and term births. Analyses stratified by child sex indicated that in both boys (HR: 1.50; 95% CI: 1.33–1.70) and girls (HR: 1.62; 95% CI: 1.28–2.05), HG exposure was associated with ASD risk and was the strongest when exposure occurred during the first two trimesters.

Our results indicated that commonly prescribed medication to treat mild forms of HG did not significantly affect ASD risk (–**Table 4**). On further examining the effect of immediate versus later in-hospital or outpatient care on ASD risk, we observed no significant difference between women who were admitted early versus late during their illness (HR: 1.24; 95% CI: 0.69–2.24; $p = 0.47$). However, we observed higher ASD risk (HR: 1.41; 95% CI: 1.05–1.90; $p = 0.02$) among children of women who received electrolyte replacement. In this sample limited to recent birth years with complete data available, HG with metabolic disturbance is still significantly associated with ASD risk (HR: 1.33; 95% CI: 1.11–1.60; $p = 0.002$); however, the magnitude of the effect is lower than that observed for the total sample.

ASD diagnoses occurred at younger ages in children exposed to HG prenatally than in those who were not (–**Fig. 1A**). Although, ASD risk was elevated in both boys and girls regardless of the severity of exposure, the relationship was strongest among girls (–**Fig. 1B**).

The incidence of ASD diagnosis was higher for HG exposed children of all racial-ethnic backgrounds. HG exposure was found to be significantly associated with ASD in whites (HR: 1.70; 95% CI: 1.23–2.36) and Hispanics (HR: 1.76; 95% CI: 1.41–2.18), but not in blacks (HR: 1.18; 95% CI: 0.77–1.81) and Asian/Pacific Islanders (HR: 1.37; 95% CI: 0.88–2.14).

The results of the sensitivity analyses after excluding children with only one ASD diagnosis, a history of developmental and emotional comorbidities, congenital malformation, excluding children aged <4 years, and accounting for “year of birth,” family predisposition to ASD, and maternal medical and obstetrical comorbidities did not differ substantially from the overall

Table 1 Distribution of maternal and child characteristics based on HG status

Characteristics	No HG <i>n</i> = 455,263 (%)	HG <i>n</i> = 14,526 (%)	<i>p</i> -Value
Maternal age (y)			<0.001
< 20	27,171 (6.0)	760 (5.2)	
20–29	196,748 (43.2)	7,348 (50.6)	
30–34	138,693 (30.5)	4,093 (28.2)	
≥ 35	92,651 (20.4)	2,325 (16.0)	
Maternal education (y)			<0.001
< 12	46,726 (10.3)	992 (6.8)	
12	128,537 (28.2)	4,459 (30.7)	
≥ 13	264,821 (58.2)	8,864 (61.0)	
Missing	15,179 (3.3)	211 (1.5)	
Median household income, USD			<0.001
< 30,000	45,228 (9.9)	1,105 (7.6)	
30,000–49,999	156,488 (34.4)	4,914 (33.8)	
50,000–69,999	135,396 (29.7)	4,432 (30.5)	
70,000–89,999	69,182 (15.2)	2,450 (16.9)	
≥ 90,000	46,127 (10.1)	1,569 (10.8)	
Nulliparous	175,982 (38.7)	5,756 (39.6)	<0.001
Smoking during pregnancy	31,126 (6.8)	834 (5.7)	<0.001
Late/no initiation of prenatal care	45,935 (10.1)	766 (5.3)	<0.001
Gestational age <37 weeks	33,133 (7.3)	1,223 (8.4)	<0.001
Child's Race/Ethnicity			<0.001
Non-Hispanic White	98,328 (21.6)	2,336 (16.1)	
Non-Hispanic Black	38,757 (8.5)	1,924 (13.2)	
Hispanic	170,416 (37.4)	5,526 (38.0)	
Asian/Pacific Islander	39,437 (8.7)	1,334 (9.2)	
Other/Multiple	102,125 (22.4)	3,346 (23.0)	
Child's sex			<0.001
Female	221,856 (48.7)	7,592 (52.3)	
Male	233,407 (51.3)	6,934 (47.7)	

Abbreviations: HG, Hyperemesis gravidarum; USD, United States dollar.

analysis (→ **Supplementary Appendix C: → Supplementary Table S1** [available in the online version]). Lastly, a sensitivity analysis using E-value to assess bias due to potential unmeasured confounders³² gave an E-value of 2.43 (95%CI: 2.08–2.79) for the overall adjusted HR of 1.53 (95%CI: 1.37–1.70). Thus, a minimum risk ratio of 2.08 would be required between unmeasured confounders and HG exposure, and between unmeasured confounders and ASD to explain away the significant association between HG and child ASD.

Discussion

In this study, we demonstrated that in utero exposure to HG is associated with increased risk of ASD that could not be explained by confounding factors. The magnitude of association did not vary with the severity of exposure and was strongest when the exposure occurred during the first two

trimesters. Exposure to HG increases ASD risk, regardless of term or preterm birth with greatest risk in the first two-thirds of pregnancy. We also found that prenatal HG increased ASD risk in boys and girls and that there were significantly increased risks for whites and Hispanics. Commonly prescribed medication for mild forms of HG did not alter ASD risk.

We hypothesized that the effect of HG on ASD is highly dependent on the timing of fetal exposure to HG because previous studies demonstrated that poor maternal nutrition during early fetal life leads to long-term neurodevelopmental impairments.^{9,33–35} However, our inability to detect HG as a cause of ASD in the third trimester may also be due to greatly reduced rates of HG in that time. Moreover, adjusting for history of prenatal psychosocial disorders, a factor linked to cognitive impairments in children,³⁶ did not affect the magnitude of association, suggesting an independent effect of HG on ASD risk.

Table 2 Association between hyperemesis gravidarum and autism spectrum disorder

Hyperemesis Gravidarum status	Number		Incidence rate ^a	Hazard ratios (95% confidence Intervals)		
	Total births	ASD		Crude	Adjusted ^b	p-Value
No HG	455,263	8115	1.71	1.0 (ref.)	1.0 (ref.)	
HG	14,526	332	2.87	1.47 (1.31–1.64)	1.53 (1.37–1.70)	<0.001
Trimester at first diagnosis						
1st trimester (weeks of gestation)	11,505	269	2.94	1.50 (1.33–1.71)	1.58 (1.40–1.79)	<0.001
2nd trimester (weeks of gestation)	2,785	59	2.68	1.36 (1.05–1.76)	1.36 (1.05–1.75)	0.02
3rd trimester (weeks of gestation)	236	4	1.80	1.01 (0.38–2.69)	1.06 (0.40–2.83)	0.91
^c Severity of illness						
HG without metabolic disturbance	8,195	183	2.77	1.42 (1.23–1.64)	1.46 (1.26–1.69)	<0.001
HG with metabolic disturbances	6,331	149	3.00	1.53 (1.30–1.80)	1.63 (1.38–1.92)	<0.001

Abbreviations: ASD, autism spectrum disorders; HG, hyperemesis gravidarum.

^aIncidence rate is shown per 1000 person-years.

^bHazard ratios (HR) were adjusted for maternal age, education, smoking during pregnancy, parity, prenatal care, maternal psychosocial disorder, child's sex, race/ethnicity, and year of diagnosis.

^cSevere metabolic disturbances that require immediate clinical intervention (injection or infusion of electrolytes, nasogastric enteral feeding, or total parenteral nutrition).

Table 3 Associations between hyperemesis gravidarum and autism spectrum disorder by gestational age at birth and child's sex

Conditions	^a Incidence rates (IR) and ^b adjusted hazard ratios (HR) for ASD											
	Preterm (n = 34,356)			Term (n = 435,433)			Female (n = 229,448)			Male (n = 240,341)		
	IR	HR (95% CI)	p-Value	IR	HR (95% CI)	p-Value	IR	HR (95% CI)	p-Value	IR	HR (95% CI)	p-Value
No HG (n = 455,263)	2.27	1.00 (ref.)		1.67	1.00 (ref.)		0.65	1.00 (Ref.)		2.73	1.00 (Ref.)	
HG (n = 14,526)	4.82	1.98 (1.48–2.66)	<0.001	2.69	1.39 (1.23–1.56)	<0.001	1.20	1.62 (1.28–2.05)	<.001	4.74	1.50 (1.33–1.70)	<0.001
Timing of 1st HG diagnosis												
1st trimester (n = 11,505)	4.73	1.95 (1.35–2.72)	<0.001	2.78	1.44 (1.26–1.64)	<0.001	1.21	1.64 (1.26–2.12)	<.001	4.94	1.57 (1.37–1.80)	<0.001
2nd trimester (n = 2785)	5.60	2.27 (1.28–4.02)	0.001	2.36	1.21 (0.91–1.61)	0.20	1.17	1.57 (0.91–2.72)	0.10	4.19	1.31 (0.98–1.75)	0.07
3rd trimester (n = 236)	0.00	–	–	1.97	1.19 (0.45–3.16)	0.73	0.89	1.36 (0.19–9.66)	0.76	2.72	0.99 (0.32–3.06)	0.98
^c Severity of illness												
HG-no metabolic disturbance	4.57	1.85 (1.23–2.77)	0.003	2.62	1.35 (1.15–1.57)	<0.001	1.58	2.15 (1.64–2.81)	<0.001	4.09	1.28 (1.08–1.53)	0.01
HG + metabolic disturbance	5.10	2.16 (1.44–3.25)	<0.001	2.78	1.45 (1.22–1.73)	<0.001	0.68	0.93 (0.58–1.48)	0.76	5.62	1.82 (1.53–2.16)	<0.001

Abbreviations: ASD, autism spectrum disorders; CI, confidence interval; HG, hyperemesis gravidarum..

^aIR, incidence rate is shown per 1,000 person-years.

^bHRs were adjusted for maternal age, education, smoking during pregnancy, perinatal care, parity, maternal psychosocial disorder, child's race/ethnicity, and year of diagnosis.

^cSevere metabolic disturbances that require immediate clinical intervention (injection or infusion of electrolytes, nasogastric enteral feeding, or total parenteral nutrition).

Although, there is increasing awareness of the fetal origins of adult disease, the long-term consequences of HG for the children are understudied. Malnutrition during pregnancy, even if limited to a few weeks or months, can lead to fetal nutrient deficiencies at a vulnerable period in organ development, increasing risk for long-term adverse health outcomes.³⁷ HG, as a cause of maternal malnutrition in early

pregnancy, may have a profound effect on fetal brain development either (1) directly, through metabolic imbalances resulted from maternal malnutrition and dehydration,³⁸ or (2) indirectly, through hypoxemia and reduced nutritional supply to the fetus by compromising placental function.^{39,40}

Women experiencing HG often have poor nutritional intake and are dehydrated, creating conditions that are

Table 4 Hyperemesis gravidarum interventions and autism spectrum disorder in children born between 2006–2014

Treatment modalities	Counts		Incidence rate ^a	Hazard ratios (95% CI)		P-value
	Total birth	ASD		Crude	Adjusted ^b	
No-HG	179,602	3,555	3.16	1.00 (ref.)	1.00 (ref.)	(Ref.) ^c
HG- without metabolic disturbance	5,538	117	3.12	1.07 (0.89–1.28)	1.13 (0.94–1.36)	0.20
No treatment	2,425	51	2.76	1.00 (ref.)	1.00 (ref.)	^c (Ref.)
Diphenhydramine	16	1	9.09	2.45 (0.34–17.67)	2.53 (0.35–18.5)	0.36
Promethazine	1,067	15	2.18	0.93 (0.59–1.46)	0.96 (0.60–1.52)	0.85
Ondansetron	1,624	25	3.67	1.04 (0.72–1.49)	1.01 (0.70–1.46)	0.95
Metoclopramide	950	29	4.45	1.41 (0.93–2.14)	1.39 (0.91–2.13)	0.12
HG with metabolic disturbances ^d	4,986	121	3.97	1.24 (1.03–1.48)	1.33 (1.11–1.60)	0.002
Inpatient care for HG as principal diagnosis	4,020	95	3.85	1.20 (0.98–1.47)	1.29 (1.05–1.58)	0.02
Treatment started on the day of diagnosis	3,550	82	3.77	1.00 (ref.)	1.00 (ref.)	^c (Ref.)
Treatment started at ≥ 1 day after diagnosis	470	13	4.44	1.19 (0.66–2.14)	1.24 (0.69–2.24)	0.47
Total enteral/parenteral nutrition	139	2	2.21	0.71 (0.18–2.85)	0.76 (0.19–3.06)	0.70
Electrolyte injection/infusion	1,798	44	4.26	1.27 (0.95–1.72)	1.41 (1.05–1.90)	0.02

Abbreviations: ASD, autism spectrum disorders; CI, confidence interval; HG, hyperemesis gravidarum.

Note: Analysis was limited to pregnancies (2006–2014) with complete medication data available in electronic medical records ($n = 190,126$).

^aIncidence rate is shown per 1,000 person-years.

^bHazard ratios were adjusted for maternal age, education, smoking during pregnancy, perinatal care, parity, maternal psychosocial disorder, child's race/ethnicity, and year of diagnosis.

^c(Ref.); reference for adjusted p -value test statistics for strata differences.

^dHG with metabolic disturbances requiring medical interventions that included injection or infusion of electrolytes, nasogastric enteral feeding, or total parenteral nutrition.

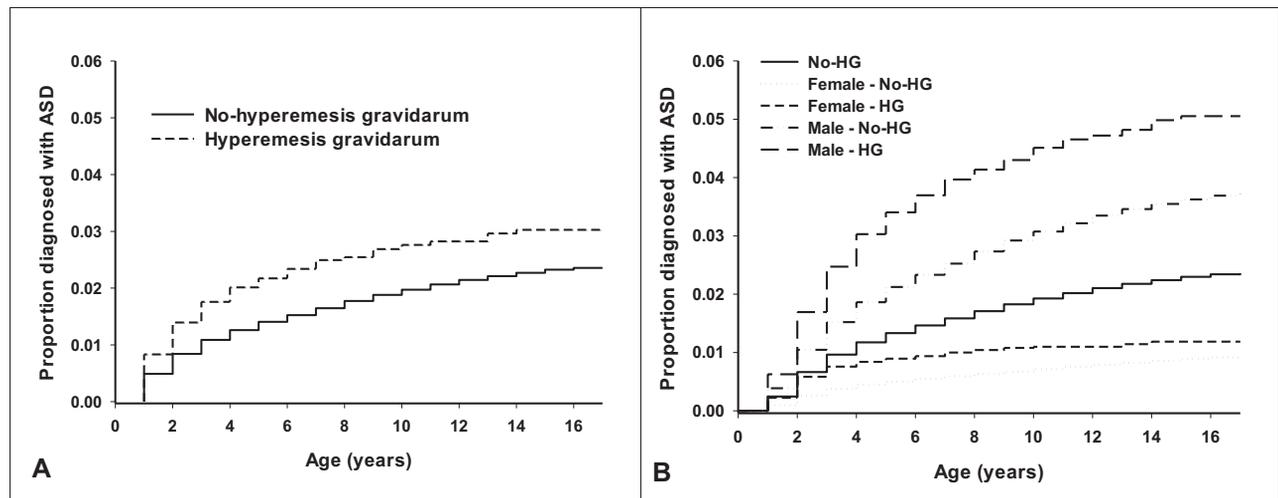


Fig. 1 Overall (A) and sex-specific (B) ASD survival curve by child age. Mean age (standard deviation [SD]) at ASD diagnosis as follows: no-HG total (5.15 [3.57]), HG total (3.87 [2.44]), no-HG male (5.12 [3.51]), HG male (4.00 [2.48]), no-HG female (5.28 [3.83]), and HG female (3.41 [2.24]). ASD, autism spectrum disorder; HG, hyperemesis gravidarum.

functionally similar to famine and may affect development in a similar manner. The best-known example is the Dutch Winter Hunger study, a natural experiment that utilized data collected on women that were forcibly deprived of food during the World War II. Caloric deprivation during the first two trimesters of pregnancy of these women increased cognitive disabilities and schizophrenia risk in the offspring.³³ Other studies have shown this effect of undernutrition on cognitive impairment may continue throughout life.⁴¹ Our finding that HG during the first two trimesters increases the ASD risk is consistent with these previous

reports. However, it is unclear how, or to what extent neurodevelopment is impaired by HG.

The placenta regulates the transfer of nutrients and oxygen from the mother to the developing fetus and can adapt morphologically and functionally to optimize nutrients and oxygen, promoting fetal organ development. Restriction of oxygen and protein clearly affects placental structure and vascularity.³⁹ Animal^{42,43} and human^{9,10} studies suggest that compromised placental function (as found in preeclampsia, GDM, and IUGR) is associated with ASD risk. Changes in placental function may also contribute to ASD development. The placenta produces

several neurodevelopmental factors, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF).⁴⁰ BDNF regulates dopaminergic neuron development whose functions are disrupted in ASD and mental retardation.^{44,45} Limiting the data to pregnancies without placental abnormalities resulted in little effect on our overall findings. This suggests that HG may have specific effects on placenta function that result in ASD or that placental functions are largely unaltered but there are fewer nutrients to transport.

The KPSC health plan approach is comprehensive and more valid than parental reporting, nonspecialist diagnosis, or case identification from records because all ASD diagnoses are confirmed by a pediatric specialist. This limits the potential for patient misclassification. Furthermore, the large size and diverse population provide opportunities to explore how risks differ by the child's sex, race/ethnicity, gestational age or timing of HG exposure. The findings add to the strong evidence that the environment that babies are exposed to in the womb is a major cause of metabolic diseases in adults. We performed several sensitivity analyses to evaluate the independent effect of prenatal exposure to HG on the observed risk relationships. Although, the magnitude of the effect is slightly lower than that observed for the full sample, we still found an association between HG and ASD after limiting the sample to recent birth years (2008–2014) that had complete data on maternal pre-pregnancy BMI and comorbidities (**→Supplementary Appendix C** [available in the online version]).

This study has potential limitations. For example, diagnostic suspicion bias can occur when exposed and unexposed patients differ in measurement (both the intensity and diagnostic process) of health outcome statuses. Perinatal exposure to maternal smoking has been linked to behavioral and cognitive impairments in children⁴⁶ and we relied on self-reported smoking during pregnancy. However, Buka, et al⁴⁷ found strong agreement between self-reported smoking and serum cotinine levels. Some medications, such as antihistamines and promethazine, may have been prescribed to suppress allergy symptoms and information was not available regarding their intended use. Moreover, dosage data on prescribed medications and other factors (e.g., environmental toxins) were not available in the electronic medical records. To better understand the potential impact these and other unmeasured confounders may have, we calculated the E-value for the main result (**→Supplementary Appendix C** [available in the online version]). Our finding suggests that the observed result would be explained by confounding bias only if the independent associations of the potential confounders with both the exposure and outcome of interest was of unrealistic magnitude (up to a 2.43-fold difference). Although causality cannot be proven based on this observational study, HG fulfills the Bradford–Hill criteria as a risk factor in terms of biological plausibility and timing.

Conclusion

Our findings provide additional evidence that the intrauterine environment has a significant impact on ASD risk. However, HG may stand out as a risk factor because it is

clinically obvious and may be useful for identifying at-risk children that may benefit from closer surveillance and earlier diagnosis. Early intervention with behavioral and developmental therapy can result in better long-term cognitive and behavioral function, and improve symptoms.⁴⁸ More aggressive diagnosis and treatment of HG may provide new opportunities to prevent this life-long disability and its impact on the families and society.

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Conflict of Interest

None declared.

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