

Congenital TORCH Infections and Neurodevelopmental Outcomes

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 Editorial

 Supplemental content

IMPORTANCE Congenital TORCH (toxoplasmosis, syphilis, rubella, cytomegalovirus, or herpes simplex) infections are established causes of severe fetal injury, yet their population-level contribution to neurodevelopmental and psychiatric outcomes, independent of familial confounding, remains yet to be quantified.

OBJECTIVE To investigate whether congenital TORCH infections are associated with neurodevelopmental and psychiatric outcomes, including autism and intellectual disability, as well as academic performance, using population-based and sibling-controlled analyses.

DESIGN, SETTING, AND PARTICIPANTS This nationwide, population-based cohort study with sibling comparisons was conducted using linked data from Swedish national health, birth, insurance, education, and death registers. Individuals born in Sweden between 1987 and 2021, including individuals diagnosed with a congenital TORCH infection, were included. Full siblings were identified for within-family comparisons. Individuals were followed up from birth until death, emigration, or December 31, 2023. Data were analyzed from November 2025 to July 2026.

EXPOSURE Clinically diagnosed congenital TORCH infections, identified from national registers, including cytomegalovirus, *Toxoplasma gondii*, rubella, and herpes simplex viruses.

MAIN OUTCOMES AND MEASURES Autism (with and without co-occurring intellectual disability), intellectual disability (by severity), attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, Tourette and chronic tic disorders, nonaffective psychosis, and standardized school grades at age 16 years were assessed. Associations were estimated with hazard ratios (HRs) using Cox regression and sibling-comparison models.

RESULTS Among 3 666 002 individuals born in Sweden, including 3 665 027 individuals without TORCH infections (1 883 911 male [51.4%]; mean [SD] follow-up, 20.50 [11.15] years) and 975 individuals with TORCH infections (532 male [54.6%]; mean [SD] follow-up, 18.70 [10.39] years), congenital TORCH infections were associated with increased risks of intellectual disability (HR, 7.22; 95% CI, 6.14-8.49) and autism (HR, 3.10; 95% CI, 2.55-3.76), with similar or greater HRs in sibling comparisons (intellectual disability: HR, 11.28; 95% CI, 5.97-21.33; autism: HR, 3.19; 95% CI, 1.97-5.15). Risks increased with greater severity of intellectual disability, with HRs ranging from 3.01; 95% CI, 2.21-4.11 for mild to 23.51; 95% CI, 18.06-30.60 for severe to profound intellectual disability) and were greater for autism with (HR, 6.23; 95% CI, 4.69-8.28) vs without (HR, 1.97; 95% CI, 1.51-2.57) co-occurring intellectual disability. No consistent associations were observed for obsessive-compulsive disorder, and associations with attention-deficit/hyperactivity disorder attenuated in sibling analyses. Individuals who were exposed had lower school grades in adolescence (TORCH-associated decrease = -1.50 points; 95% CI, -2.60 to -0.40 points).

CONCLUSIONS AND RELEVANCE In this study, congenital TORCH infections were rare but associated with intellectual disability and autism, with evidence of broader associated cognitive outcomes extending beyond diagnosed conditions, underscoring the importance of preventing specific vertically transmitted infections.

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Congenital TORCH (toxoplasmosis, syphilis, rubella, cytomegalovirus, or herpes simplex) infections comprise a group of vertically transmitted pathogens (classically, *Toxoplasma gondii*, other infections [eg, syphilis and HIV], rubella, and cytomegalovirus [CMV], and herpes simplex viruses [HSVs]) that are associated with adverse fetal and neonatal outcomes.¹ Unlike most infectious agents, TORCH pathogens can cross the placenta and infect the developing fetus, increasing risks of miscarriage, stillbirth, and pregnancy complications.² They are established causes of intellectual disability (ID) and have also been investigated in association with neurodevelopmental and psychiatric outcomes, including autism and nonaffective psychoses.³⁻⁶

Despite this, the population-level burden of TORCH infections remains poorly quantified. In contrast, studies of common maternal infections during pregnancy have reported modest associations with neurodevelopmental outcomes that are largely attenuated in genetically informed and family-based study designs.⁷⁻⁹ This suggests that such associations are primarily explained by shared familial factors rather than direct causal effects, underscoring the importance of sibling comparisons.¹⁰ To our knowledge, no prior study has applied this approach to congenital TORCH infections.

We therefore investigated associations between registered congenital TORCH infections and neurodevelopmental outcomes in 3.7 million individuals born in Sweden. Using nationwide register data beginning in 1987, including nearly 1000 individuals who were exposed, we provide population-based estimates with long-term follow-up and incorporate sibling comparisons to address familial confounding.

Key Points

Question Are congenital TORCH (toxoplasmosis, syphilis, rubella, cytomegalovirus, or herpes simplex) infections associated with neurodevelopmental and psychiatric outcomes?

Findings In this cohort study of 3 666 002 individuals born in Sweden, including 975 who were exposed, TORCH infections were associated with intellectual disability and autism in population analyses and sibling comparisons, with markedly higher risks for severe intellectual disability and autism with co-occurring intellectual disability.

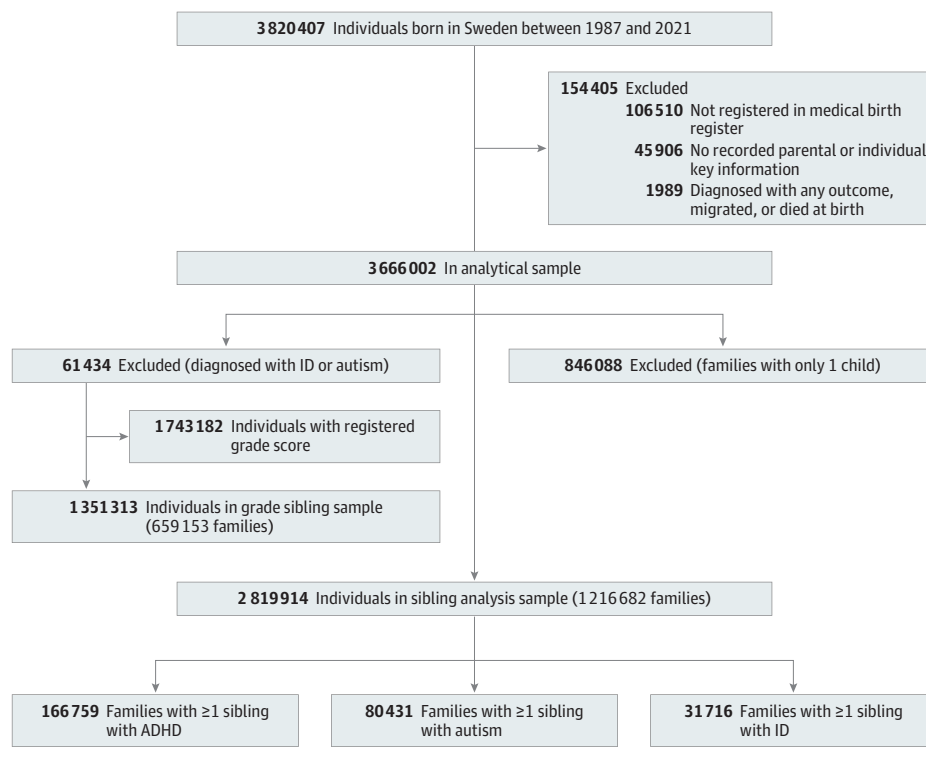
Meaning This study found that congenital TORCH infections had associations with intellectual disability and autism, underscoring the importance of strengthening global vaccination programs and other preventive strategies.

Methods

Study Cohort

In this cohort study, the selected population was 3 820 407 individuals born in Sweden between 1987 and 2021. We excluded 1 065 10 individuals who lacked a Medical Birth Register (MBR) record, 45 909 who had no recorded parental identification or regional birth information, and 1985 who migrated or died at birth. The final sample included 3 666 002 births (**Figure 1**). This study is reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline. In accordance

Figure 1. Study Flowchart



The analytical sample (3 666 002 births) is the sample used for the general population-based analyses, and the sibling samples are those used for each respective outcome. The grade score analyses included 1 743 182 births in the general population and 1 351 313 sibling-births. ADHD indicates attention-deficit/hyperactive disorder; ID, intellectual disability; OCD, obsessive-compulsive disorder.

Table 1. Distribution of Covariates by Exposure to Diagnosed Congenital TORCH Infection

	Individuals, No. (%)		
Covariate	No TORCH infection (n = 3 665 027)	TORCH infection (n = 975)	P value ^a
No registered grades (born 1987-2005, without autism or ID)			
No	1 742 772 (95.3)	420 (85.5)	<.001
Yes	86 701 (4.7)	71 (14.5)	
Birth order			
1	1 545 746 (42.2)	461 (47.3)	.01
2	1 344 702 (36.7)	332 (34.1)	
3	536 063 (14.6)	117 (12.0)	
4	156 794 (4.3)	45 (4.6)	
≥5	81 722 (2.2)	20 (2.1)	
Year of birth			
1987-1993	801 823 (21.9)	332 (34.1)	<.001
1994-2000	646 709 (17.6)	199 (20.4)	
2001-2007	679 722 (18.5)	137 (14.1)	
2008-2014	761 235 (20.8)	160 (16.4)	
2015-2021	775 538 (21.2)	147 (15.1)	
Season of birth			
Dec to Feb	855 878 (23.4)	248 (25.4)	.36
Mar to May	988 582 (27.0)	262 (26.9)	
Jun to Aug	963 922 (26.3)	255 (26.2)	
Sep to Nov	856 645 (23.4)	210 (21.5)	
Sex			
Female	1 781 116 (48.6)	443 (45.4)	.048
Male	1 883 911 (51.4)	532 (54.6)	
Preeclampsia			
No	3 555 689 (97.0)	916 (93.9)	<.001
Yes	109 338 (3.0)	59 (6.1)	
Cesarean delivery			
No	3 398 713 (92.7)	830 (85.1)	<.001
Yes	266 314 (7.3)	145 (14.9)	
Low Apgar score (5 min after birth)			
≥7	3 592 274 (98.0)	878 (90.1)	<.001
<7	41 908 (1.1)	77 (7.9)	
Missing	30 845 (0.8)	20 (2.1)	
Gestational age			
Preterm	212 121 (5.8)	307 (31.5)	<.001
Term	2 553 697 (69.7)	536 (55.0)	
Late term	653 230 (17.8)	92 (9.4)	
Post term	243 176 (6.6)	36 (3.7)	
Missing	2803 (0.1)	4 (0.4)	
Size for gestational age			
Normal	3 346 787 (91.3)	732 (75.1)	<.001
Small	83 142 (2.3)	131 (13.4)	
Large	125 926 (3.4)	35 (3.6)	
Missing	109 172 (3.0)	77 (7.9)	

(continued)

with established practice for Swedish register-based research, the need for individual informed consent was waived by the Stockholm regional ethical review committee and the Swedish Ethical Review Authority because the study involved no direct contact with participants and used routinely collected register data under ethical approval and appropriate safeguards for confidentiality (ethical approvals: DNR 2010-1185-31-5, with amendments DNR 2020-05640, DNR 2022-02662-02, and DNR 2024-00930-02).

Exposures

Our exposure (ie, congenital TORCH infections) was first extracted from the MBR (eTable 1 in [Supplement 1](#)), supplemented from other register sources (National Patient Register and National Insurance Register) given that some perinatal and congenital diagnoses are made retrospectively (eg, by observing hearing loss later in life and identifying CMV DNA in archived dried blood spots from the neonatal screening program¹¹). Diagnostic methods of TORCH

Table 1. Distribution of Covariates by Exposure to Diagnosed Congenital TORCH Infection (continued)

	Individuals, No. (%)		
Covariate	No TORCH infection (n = 3 665 027)	TORCH infection (n = 975)	P value ^a
Mother's BMI			
Normal weight (18.5 to <25)	2 125 630 (58.0)	539 (55.3)	<.001
Underweight (<18.5)	101598 (2.8)	33 (3.4)	
Overweight (25 to <30)	816238 (22.3)	201 (20.6)	
Obesity (≥30)	374 247 (10.2)	89 (9.1)	
Missing	247 314 (6.7)	113 (11.6)	
Paternal age, y			
<25	233 353 (6.4)	90 (9.2)	<.001
25-29	848 687 (23.2)	253 (25.9)	
30-34	1 230 150 (33.6)	311 (31.9)	
35-39	835 458 (22.8)	191 (19.6)	
>39	517 379 (14.1)	130 (13.3)	
Maternal age			
<25	520 475 (14.2)	190 (19.5)	<.001
25-29	1 157 527 (31.6)	303 (31.1)	
30-34	1 232 092 (33.6)	299 (30.7)	
35-39	611 977 (16.7)	152 (15.6)	
>39	142 956 (3.9)	31 (3.2)	
Highest attained parental education, y			
<10	137 106 (3.7)	41 (4.2)	.15
10-12	536 979 (14.7)	165 (16.9)	
>12	2 913 446 (79.5)	746 (76.5)	
Missing	77 496 (2.1)	23 (2.4)	
Paternal psychiatric diagnosis			
No	3 161 083 (86.2)	826 (84.7)	.16
Yes	503 944 (13.8)	149 (15.3)	
Maternal psychiatric diagnosis			
No	3 001 223 (81.9)	757 (77.6)	<.001
Yes	663 804 (18.1)	218 (22.4)	
Paternal origin			
Sweden	2 886 026 (78.7)	757 (77.6)	.93
Europe	142 005 (3.9)	35 (3.6)	
East Europe and Russia	144 904 (4.0)	43 (4.4)	
North America and Oceanic	23 239 (0.6)	5 (0.5)	
South America	37 261 (1.0)	11 (1.1)	
Asia	71 946 (2.0)	19 (1.9)	
Middle East and North Africa	263 510 (7.2)	81 (8.3)	
Sub-Saharan Africa	95 598 (2.6)	24 (2.5)	
Unknown	538 (<1)	0 (0.0)	
Maternal origin			
Sweden	2 917 010 (79.6)	782 (80.2)	.95
Europe	123 326 (3.4)	25 (2.6)	
East Europe and Russia	155 814 (4.3)	44 (4.5)	
North America and Oceanic	16 445 (0.4)	5 (0.5)	
South America	34 505 (0.9)	10 (1.0)	
Asia	109 278 (3.0)	31 (3.2)	
Middle East and North Africa	221 347 (6.0)	57 (5.8)	
Sub-Saharan Africa	87 012 (2.4)	21 (2.2)	
Unknown	290 (<0.1)	0)	

Abbreviations: ADHD, attention-deficit/hyperactive disorder; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ID, intellectual disability; TORCH, toxoplasmosis, syphilis, rubella,

cytomegalovirus, or herpes simplex.

^a All reported P values are from the χ^2 -test.

Table 2. Unadjusted Incidence Rates for Individuals With and Without Congenital TORCH Infection Diagnosis

Diagnosis	TORCH infection		No TORCH infection		Between-group difference (95% CI)
	Cases/person-years	Rate per 1000 person-years (95% CI)	Cases/person-years (95% CI)	Rate per 1000 person-years	
Any ADHD	90/19 192	4.69 (3.81 to 5.77)	255 642/66 828 564	3.83 (3.81 to 3.84)	0.86 (−0.11 to 1.83)
Autism					
Any	102/18 913	5.39 (4.44 to 6.55)	115 827/67 712 066	1.71 (1.70 to 1.72)	3.68 (2.64 to 4.72)
With ID	48/19 365	2.48 (1.87 to 3.29)	18 642/68 369 098	0.27 (0.27 to 0.28)	2.21 (1.51 to 2.91)
Without ID	54/19 536	2.76 (2.12 to 3.61)	97 185/67 908 549	1.43 (1.42 to 1.44)	1.33 (0.59 to 2.07)
ID					
Any	148/18 012	8.22 (6.99 to 9.65)	46 063/68 065 065	0.68 (0.67 to 0.68)	7.54 (6.22 to 8.86)
Mild	40/19 503	2.05 (1.50 to 2.80)	29 078/68 267 914	0.43 (0.42 to 0.43)	1.62 (0.98 to 2.26)
Moderate	30/19 599	1.53 (1.07 to 2.19)	7138/68 490 506	0.10 (0.10 to 0.11)	1.43 (0.88 to 1.98)
Severe	44/19 566	2.25 (1.67 to 3.02)	2625/68 537 386	0.04 (0.04 to 0.04)	2.21 (1.55 to 2.87)
Profound	15/19 814	0.76 (0.46 to 1.26)	1065/68 553 547	0.02 (0.01 to 0.02)	0.74 (0.36 to 1.12)
Unspecified	19/19 763	0.96 (0.61 to 1.51)	6157/68 505 378	0.09 (0.09 to 0.09)	0.87 (0.44 to 1.30)
Moderate to profound	89/19 002	4.68 (3.81 to 5.77)	10 828/68 450 278	0.16 (0.16 to 0.16)	4.52 (3.55 to 5.49)
Severe to profound ID	59/19 392	3.04 (2.36 to 3.93)	3690/68 525 352	0.05 (0.05 to 0.06)	2.99 (2.21 to 3.77)
Any OCD	10/19 925	0.50 (0.27 to 0.93)	33 913/68 321 606	0.50 (0.49 to 0.50)	0.00 (−0.31 to 0.31)
Any ToTD	<5/19 957 ^a	NA ^a	17 657/68 403 539	0.26 (0.25 to 0.26)	NA ^a
Any NAP	8/19 937	0.40 (0.20 to 0.80)	16 035/68 454 424	0.23 (0.23 to 0.24)	0.17 (−0.11 to 0.45)

Abbreviations: ADHD, attention-deficit/hyperactive disorder; ID, intellectual disability; NA, not applicable; NAP, nonaffective psychosis; OCD, obsessive-compulsive disorder; TORCH, toxoplasmosis, syphilis, rubella,

cytomegalovirus, or herpes simplex; ToTD, tics or Tourette disorder.

^a Censored due to fewer than 5 exposed cases.

changed over time, with increasing degrees of precision (eTable 3 in Supplement 1).

Outcomes

The neurodevelopmental and psychiatric outcomes were autism spectrum disorder (hereafter, *autism*), attention-deficit/hyperactive disorder (ADHD), ID, obsessive compulsion disorder (OCD), Tourette or chronic tic disorders, and any nonaffective psychosis (eTable 2 in Supplement 1), ascertained from the National Patient Register, National Insurance Register, and Cause of Death Register. Autism was stratified into autism with or without ID. We examined subtypes of ID (mild, moderate, severe, profound, and unspecified) and aggregated these subtypes in some analyses due to lack of power (eg, combining severe and profound ID into 1 group).

To investigate whether TORCH infection may also have more subtle associations with cognitive abilities, not necessarily associated with a diagnosed neurodevelopmental or psychiatric condition, we used grades at the end of mandatory schooling at age 16 years, standardized within each year and rescaled to a more intuitive distribution (mean [SD], 100 [15] points). In the grades analysis, the sample was restricted to individuals born before 2006 and not diagnosed with a neurodevelopmental condition associated with cognitive performance (autism or ID).

Covariates

We included covariates that have previously been associated with both infections and neurodevelopmental outcomes (eTables 1-2 in Supplement 1).^{7,9} Parental region of origin was included as a potential confounder to account for notable geographic differences in the prevalence of exposure to TORCH agents and the differential likelihood of diagnosis with neurodevelopmental

conditions among migrant groups in Sweden compared with those whose parents were born in Sweden.

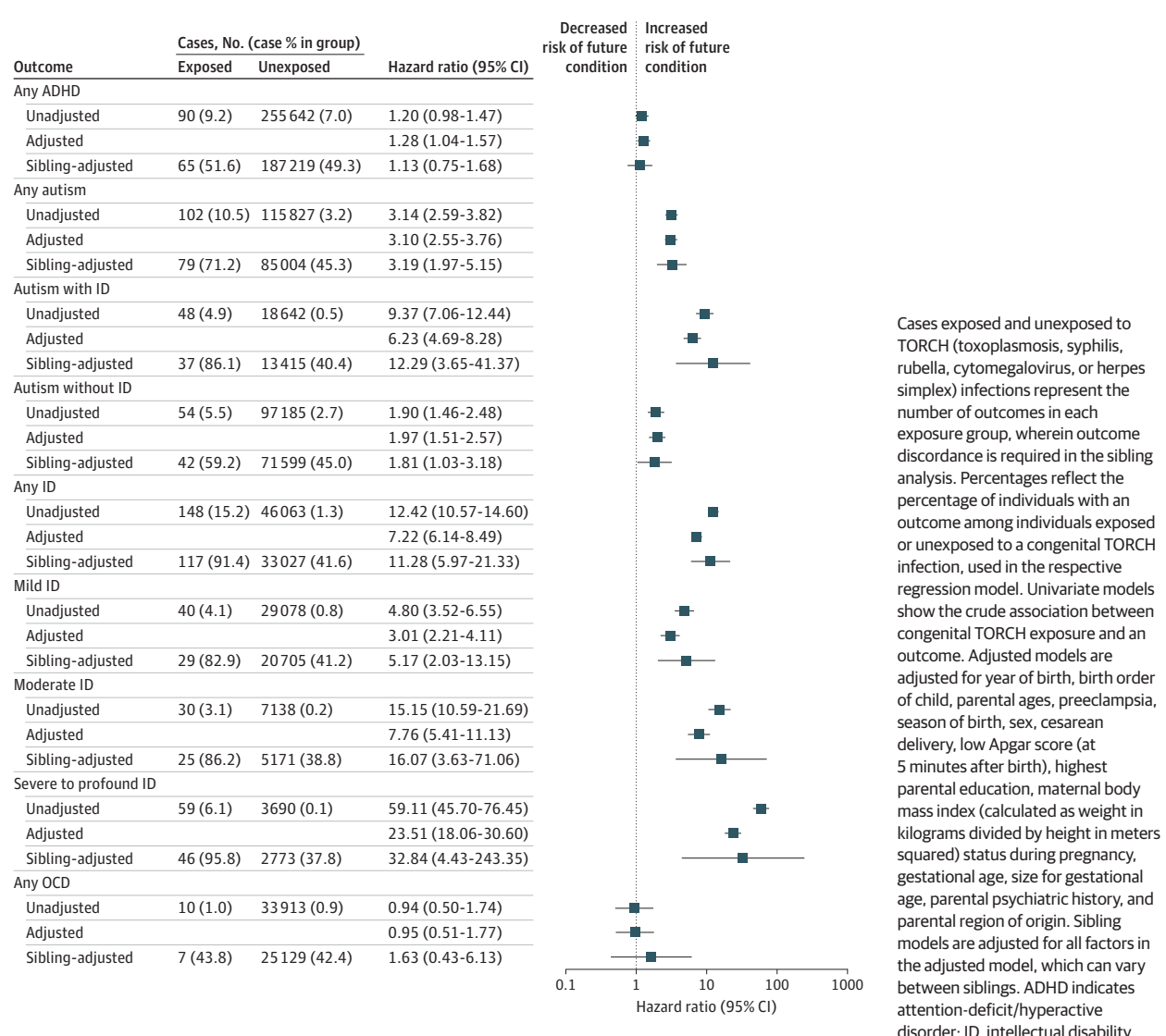
We also considered the following covariates measured at the time of birth (from the MBR): preeclampsia, cesarean delivery, low Apgar score (5 minutes after birth), gestational age, and size for gestational age. Although measured temporally before infections were ascertained, these could act as potential mediators of any association of TORCH infections (eTable 4 in Supplement 1). Including them in models leads to a more conservative estimation of risk.

Statistical Analysis

Cox regression model hazard ratios (HRs) were estimated following up the study population from birth and until death (Cause of Death Register), emigration, or end of follow-up (December 31, 2023) using the individual's age as the underlying time scale. Models did not account for several outcomes simultaneously unless directly specified (ie, severity of ID). Sibling models were estimated using the conditional likelihood estimation, conditioning on the biological nuclear family (ie, comparing full siblings). Only regression models that contained at least 10 exposed cases were reported. For grade scores, we used generalized least squares regression models, with random effects for population analyses (assuming individual-specific effects normally distributed and uncorrelated with regressors) and fixed effects (within estimator) models for sibling analyses. Individuals with ID, autism, or both were excluded from grade analyses. Whenever possible, we also examined specific TORCH infections separately to investigate their specific associations with our study outcomes.

We present crude and adjusted estimates, including all previously described covariates. To put the rarity of TORCH into context, we calculated numbers needed to harm or treat and attributable fractions.¹²

Figure 2. Forest Plot of Associations Between Infection and Risks for Future Neurodevelopmental Conditions



We also fitted a partially adjusted model excluding potential mediators given that these factors may lie on the causal pathway between fetal infection and later outcomes. Finally, we limited the exposure to TORCH infections diagnosed only during the first year of life to guard against surveillance bias.

All analyses were estimated using Stata/MP statistical software version 17.0 (StataCorp). The significance level was set at $P < .05$, and we used 2-sided tests. Data were analyzed from November 2025 to July 2026.

Results

Among 3 666 002 individuals, 3 665 027 individuals (1 883 911 male [51.4%] male; mean [SD] follow-up, 20.50 [11.15] years) did not have and 975 (532 male [54.6%]; mean [SD] follow-up, 18.70 [10.39] years) had a registered congenital TORCH infection, corresponding to 2.5 per 10 000 births

overall. The mean (SD) age at follow-up for the overall population was 19 (10.4) years. There were even lower infection rates after the mid-1990s, when rubella virtually disappeared in Sweden after the introduction of national vaccination. Exposure to CMV, *T gondii*, and HSV infections remained stable over time, although fewer than 10 individuals annually were diagnosed with HSV or *T gondii*, compared with 10 to 20 individuals with CMV. CMV accounted for approximately half of all TORCH cases (487 individuals [49.9%]) and occurred at a rate of 1 to 2 cases per 10 000 births (eTable 5 in Supplement 1).

Individuals who were exposed to TORCH infections were more likely than those who were unexposed to be missing grade data at age 16 years (71 individuals [14.5%] vs 86 701 individuals [4.7%]; $P < .001$). TORCH infections were more likely to occur with obstetric complications (eg, born preterm) (Table 1). The incidence of several neurodevelopmental outcomes was higher among individuals with TORCH infections than individuals in

Table 3. Associations Between Registered Congenital TORCH Infection and School Grades^a

Infection	Difference (95% CI), points ^b				
	Unadjusted model	Partially adjusted	Fully adjusted	Partially adjusted sibling	Fully adjusted sibling
Any TORCH infection	-1.147 (-2.336 to 0.042)	-1.643 (-2.742 to -0.543)	-1.500 (-2.599 to -0.401)	-1.368 (-2.846 to 0.110)	-1.355 (-2.833 to 0.124)
Specific TORCH infections					
<i>Toxoplasma gondii</i>	-2.435 (-6.917 to 2.048)	-4.033 (-8.185 to 0.119)	-3.720 (-7.871 to 0.430)	-4.531 (-9.982 to 0.920)	-4.331 (-9.781 to 1.119)
Other	0.243 (-1.600 to 2.086)	-0.162 (-1.865 to 1.541)	-0.010 (-1.713 to 1.692)	1.093 (-1.222 to 3.407)	1.074 (-1.241 to 3.389)
Rubella	-3.964 (-7.237 to -0.691)	-4.860 (-7.898 to -1.832)	-5.044 (-8.081 to -2.006)	-5.818 (-9.672 to -1.963)	-5.938 (-9.793 to -2.084)
Cytomegalovirus	-1.938 (-4.091 to 0.215)	-2.140 (-4.130 to -0.151)	-1.854 (-3.844 to 0.135)	-2.850 (-5.540 to -0.160)	-2.759 (-5.448 to -0.069)
Herpes simplex	-4.099 (-9.789 to 1.590)	-4.695 (-9.963 to 0.573)	-4.600 (-9.866 to 0.667)	-0.970 (-7.929 to 5.989)	-0.956 (-7.913 to 6.002)
Syphilis	0.744 (-4.105 to 5.594)	1.112 (-3.354 to 5.578)	1.160 (-3.304 to 5.625)	1.264 (-5.128 to 7.656)	1.301 (-5.090 to 7.691)

Abbreviation: TORCH, toxoplasmosis, syphilis, rubella, cytomegalovirus, or herpes simplex.

^a The population mean (SD) school grade was 100 (15) points.

^b Individuals with diagnosed intellectual disability or autism before the end of follow-up were excluded. Unadjusted models show the crude association between exposure and outcome. Partially adjusted models are adjusted for year of birth, birth order of child, parental ages, season of birth, sex, highest parental education, maternal body mass index status during pregnancy,

parental psychiatric history, and parental region of origin. Fully adjusted models are adjusted for the same covariates but also include preeclampsia, cesarean delivery, low Apgar score (5 minutes after birth), gestational age, and size for gestational age. Adjusted sibling models are adjusted for all factors in the partially adjusted model, which can vary between siblings. The fully adjusted sibling model is adjusted for all factors in the adjusted sibling model but also includes preeclampsia, cesarean delivery, low Apgar score (5 minutes after birth), gestational age, and size for gestational age.

the unexposed population (Table 2). Autism was diagnosed with a rate of 5.39 diagnoses (95% CI, 4.44-6.55 diagnoses) per 1000 person-years among individuals who were exposed vs 1.71 diagnoses (95% CI, 1.70-1.72 diagnoses) in those who were unexposed, while rates for ID were 8.22 diagnoses (95% CI, 6.99-9.65 diagnoses) vs 0.68 diagnoses (95% CI, 0.67-0.68 diagnoses), respectively. ADHD was slightly more common among individuals who were exposed (4.69 diagnoses; 95% CI, 3.81-5.77 diagnoses vs 3.83 diagnoses; 95% CI, 3.8-3.84 diagnoses). OCD was similar across groups, at approximately 0.5 diagnoses per 1000 person years (0.50 diagnoses; 95% CI, 0.27-0.93 diagnoses in exposed vs 0.50 diagnoses; 95% CI, 0.49-0.50 diagnoses in unexposed populations). There were fewer than 10 individuals in the exposed group with Tourette or chronic tic disorders or with non-affective psychosis (8 individuals), precluding further analyses of these outcomes.

Intellectual Disability

We observed a high risk for ID in the adjusted population model (HR, 7.22; 95% CI, 6.14-8.49) and sibling model (HR, 11.28; 95% CI, 5.97-21.33). Having a TORCH infection was associated with an increased risk for all ID subtypes; the HR was 3.01 (95% CI, 2.21-4.11) for mild, 7.76 (95% CI, 5.41-11.13) for moderate, and 23.51 (95% CI, 18.06-30.60) for severe to profound ID. Associations with similar or higher HRs were observed in sibling comparisons (Figure 2; eTable 6 in Supplement 1).

TORCH infections were responsible for increasingly larger proportions of cases as the severity of ID increased. The attributable fraction was 0.073% (95% CI, 0.042%-0.104%) for mild ID, 0.304% (95% CI, 0.193%-0.415%) for moderate ID, and 1.248% (95% CI, 0.973%-1.522%) for profound to severe ID (eTable 7 in Supplement 1).

Autism

The risk of autism was increased among individuals with TORCH infections (HR, 3.10; 95% CI, 2.55-3.76), with a simi-

larly increased risk observed when comparing siblings (HR, 3.19; 95% CI, 1.97-5.15). HRs for the association of TORCH infections with autism were higher for with autism with ID than autism without ID in population-based models (HR, 6.23; 95% CI, 4.69-8.28 vs 1.97; 95% CI, 1.51-2.57) and sibling models (HR, 12.29; 95% CI, 3.65-41.37 vs 1.81; 95% CI, 1.03-3.18) (Figure 2). While TORCH infections would hypothetically be responsible for only 0.034% (95% CI, 0.027%-0.041%) of diagnosed autism cases, we would expect every fifth individual exposed to a TORCH infection to develop autism (eTable 7 in Supplement 1).

ADHD and OCD

While the population-based model indicated an association of TORCH infections with an increased risk for ADHD (HR, 1.28; 95% CI, 1.04-1.57), the association disappeared in the sibling model (Figure 2). TORCH infections were not associated with OCD in population-based analyses or sibling comparisons (Figure 2).

School Grades

A total of 420 individuals were diagnosed with a TORCH infection but not autism or ID and had a grade score at the end of mandatory schooling. Among these individuals, a TORCH infection was associated with a decrease of -1.50 points (95% CI, -2.60 to -0.40 points) in school grades. A similar, but not statistically significant decrease was observed in the sibling model (-1.36 points; 95% CI, -2.83 to 0.12 points) (Table 3).

Specific TORCH Infections

CMV, other, *T gondii*, and syphilis infections were associated with autism in population-based models, with HRs ranging from 1.66 (95% CI, 1.00-2.75) for other to 4.57 (95% CI, 3.63-5.75) for CMV. Similar associations of other infections and CMV with au-

tism risk were observed in sibling comparisons (eTable 8 in Supplement 1).

Among the different diagnosed TORCH infections, all groups with a sufficient number of exposed cases (≥ 5 cases) were associated with ID in population-based models. Sibling comparisons indicated associations with similar or even larger HRs for CMV, HSV, and other infections (eTable 8 in Supplement 1).

Associations of specific infections with grade scores varied. Rubella was associated with a 5.04-point reduction (95% CI, 2.01-8.08 points) in grade scores in the population, consistent with the sibling comparison. CMV was associated with a 2.76-point reduction (95% CI, 0.07-5.45 points) in sibling models, with similar point estimates observed in the population. We did not observe associations between *T gondii*, other, HSV, or syphilis infections and grade scores (Table 3).

CMV was associated with ADHD in the population analysis but not in the sibling analysis. No other infections exhibited any association with ADHD (eTable 8 in Supplement 1).

Additional Analyses

Excluding potential mediators from analyses did not affect the association with grade scores substantially (Table 3). Risk estimates for most diagnoses were higher in the partially adjusted model; for example, an HR of 58.34 (95% CI, 45.09-75.49) was observed in the partially adjusted model for severe to profound ID (eTable 9 in Supplement 1) compared with 23.51 (18.06-30.60) observed in the fully adjusted model (Figure 2). Results remained consistent when we included TORCH infections diagnosed within the first year of life (eTable 10 in Supplement 1).

Discussion

To our knowledge, this cohort study provides the first population-based estimates of associations between congenital TORCH infections and neurodevelopmental and psychiatric outcomes, using Swedish register data. We observed strong and robust associations with autism and ID but not with ADHD or OCD. We also observed that individuals exposed to TORCH infections had lower academic performance in adolescence, even in the absence of diagnosed autism or ID. By incorporating sibling comparisons, we accounted for potential familial confounding, a key limitation of observational studies. Our findings suggest that TORCH infections may represent a rare example of perinatal environmental risk factors, providing evidence toward a consistent association with autism and ID.¹⁰

Intellectual Disability

Although ID was originally described as a feature of congenital TORCH infections,¹³ contemporary population-based evidence remains sparse, largely limited to small clinical samples with limited control for confounding.¹⁴ Our findings provide strong evidence that TORCH infections are rare but severe environmental factors associated with ID. Associations were highly consistent between sibling and population-based models, indicating minimal confounding by shared familial factors. Variation across levels of ID severity is a novel finding yet aligns with

previous reports of heterogeneous outcomes. Observed gradients across severity further suggest increasing etiological contributions with greater severity. Nevertheless, attributable risk estimates indicate that TORCH infections accounted for only a small proportion of ID cases in the population.

Autism

Compared with ID, evidence associating TORCH infections with autism is less established. Autistic features were first described in children with congenital rubella.¹⁵ Later studies reported that 12% to 15% of children with congenital rubella syndrome met the criteria for autism.¹⁶ However, the rarity of rubella in vaccinated populations limits firm conclusions. We observed some associations with continuous measures of academic achievement, indicating that congenital rubella infections may have the potential to subtly contribute to neurodevelopmental outcomes. The steep decline in the prevalence of rubella infections after 1990, when national vaccination programs were introduced, highlights the public health importance of developing, deploying, and maintaining mass vaccination strategies to prevent congenital TORCH infections and their potential downstream outcomes.

Evidence for CMV has largely come from small clinical samples and case reports with few exposed cases.¹⁷⁻²⁰ A meta-analysis of 3 small case-control studies (5 exposed cases in total) reported a markedly elevated risk of autism, although with considerable uncertainty.²¹ More recently, a 2018 US Medicaid study reported an approximately 2.5-fold increased risk of autism after congenital CMV infection,⁵ although this study did not include sibling comparisons or account for co-occurring ID.

We found that TORCH infections were robustly associated with increased autism risk. Given the frequent co-occurrence of autism and ID, this raises the question of whether associations were driven by ID. Associations had greater HRs for autism with co-occurring ID than without, although both remained robust in sibling analyses. In contrast to studies of common maternal infections, where associations with autism are largely explained by familial confounding,^{7,8,22} our findings persisted after sibling adjustment. Nevertheless, absolute risk estimates indicate that these exposures accounted for only a small proportion of autism cases in the population.

Other Clinical Outcomes

While TORCH infections showed clear associations with ID and autism, other clinical outcomes showed limited or no evidence of association. To our knowledge, only 1 study has examined TORCH infections in association with ADHD symptoms,²³ and ours is the first to assess clinically diagnosed ADHD. Any weak population-level association was attenuated in sibling models, suggesting confounding by shared familial factors, consistent with patterns observed for common maternal infections.²²

To our knowledge, no prior studies have specifically examined TORCH infections in association with OCD or Tourette and chronic tic disorders. However, these outcomes have been included in studies of common maternal infections,^{9,22} often showing patterns similar to that of autism. Our findings do not support associations with TORCH infections.

Maternal infections with *T gondii*, HSV, and CMV have been associated with schizophrenia in prior studies based on antibody measures.²⁴ In our cohort, only 8 individuals who were exposed developed nonaffective psychosis, and the relatively young age at follow-up (mean, 19 years) limited power to detect this rare outcome. However, even under conservative assumptions, the number of observed cases was lower than expected if TORCH infections had associations comparable to those seen for ID or autism. We would expect to observe 31 individuals with nonaffective psychosis among the group exposed to TORCH if the true relative risk for nonaffective psychosis after exposure to TORCH was 7.22 (as observed for ID) or 13 individuals if the true relative risk was 3.10 (as observed for autism). Together, these findings do not support a role for congenital TORCH infections in nonaffective psychosis.

School Grades

Given the variable cognitive outcomes associated with TORCH infections, which are not always associated with ID, we examined whether these exposures were associated with more subtle deficits. Prior evidence is limited to a few small clinical studies of children without overt ID, with inconclusive findings.^{25,26} In our study, TORCH infections were associated with lower grade scores in the population, although sibling estimates were imprecise, limiting firm conclusions.

Analyses of specific infections indicated negative associations for rubella and CMV, suggesting heterogeneity across TORCH infections. The persistence of these associations in sibling comparisons indicates a limited likelihood of confounding by shared familial factors. Together, these findings suggest that TORCH exposures may be associated with lasting cognitive performance outcomes into adolescence, even in the absence of diagnosed neurodevelopmental conditions.

In the Swedish A through F grading system, rubella exposure corresponded to a reduction from an A to a F in a single subject. Alternatively, the point change could reflect a 1-letter grade reduction across half of all subjects (eg, changing from B's to C's in 8 subjects).

Strengths and Limitations

To our knowledge, this is the largest population-based study to date examining TORCH infections in association with neurodevelopmental and psychiatric outcomes, with up to 36 years of follow-up and assessment of school performance at age 16 years. Strengths include nationwide register data, which minimize selection and recall bias and enable long-term follow-up across multiple outcomes. The large cohort allowed study of a rare exposure with sufficient power for several outcomes and estimation of both absolute and relative risks. Sibling comparison models provide evidence that these associations are robust to confounding by shared familial factors. Additionally, the inclusion of both clinical diagnoses and continuous measures of cognitive performance provides a more comprehensive assessment, capturing outcomes below diagnostic thresholds.

The study also has several limitations. Our study was limited to clinically diagnosed, symptomatic TORCH infections. Newborn screening for TORCH is not implemented in Sweden, so we could not assess outcomes among asymptomatic cases, as studies from settings with CMV screening have suggested.²⁷ Approximately 200 infections were diagnosed after the first year of life, potentially reflecting detection after other conditions (eg, hearing loss) and raising concerns about surveillance bias; however, sensitivity analyses excluding these cases did not materially alter results.

Some diagnoses were not consistently coded across *International Classification of Diseases, Ninth Revision (ICD-9)* and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* versions. In particular, the ICD-9 code for *other* TORCH infections includes listeria, toxoplasmosis, and HSV, but also malaria and tuberculosis, which could lead to underestimation of associations before 1997. However, given the rarity of the latter infections in Sweden, any bias is likely minimal. Other agents (eg, Zika and SARS-COV-2) may exhibit similar associations^{28,29} but were not investigated in this study due to geographical and cohort restrictions.

TORCH infections are also associated with pregnancy and birth complications,³⁰ which may lie on the causal pathway. Because timing of infection relative to these factors could not be established using dates within the registers, we included them in fully adjusted models to obtain conservative estimates. This may have attenuated some associations, particularly for ID, while having little impact on other outcomes. Sensory impairments caused by the infection may also mediate some of these more subtle associations of CMV, for example, with cognition. We could not assess whether treatment of congenital infections was associated with the outcomes.

Conclusions

In line with long-standing clinical observations, this cohort study's findings support the association of symptomatic congenital TORCH infections with ID, with higher HRs for more severe forms. TORCH infections also appeared to contribute to autism, primarily driven by cases with co-occurring ID. However, despite these substantial relative risks, the population-level outcome was modest, and elimination of TORCH infections would prevent only a smaller proportion of cases in Sweden. We further found evidence of adverse outcomes in cognitive performance, reflected in lower academic achievement even in the absence of diagnosed autism or ID. In contrast, we found no support for associations with ADHD or OCD.

Together with prior studies of common maternal infections during pregnancy, these findings suggest that only specific pathogens known for their neurotropism and capability of infecting the fetus during gestation may play a role in neurodevelopmental impairment. Characterizing the full spectrum of consequences of symptomatic and asymptomatic congenital TORCH infections should be a research priority. These results also underscore the importance of strengthening preventive strategies, particularly for CMV and in settings with higher rates.

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