Autism Spectrum Disorder Diagnoses and Congenital Cytomegalovirus

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abstract

OBJECTIVE: To examine the association between congenital cytomegalovirus (cCMV) and autism spectrum disorder (ASD) administrative diagnoses in US children.

METHODS: Cohort study using 2014 to 2020 Medicaid claims data. We used diagnosis codes to identify cCMV (exposure), ASD (outcome), and covariates among children enrolled from birth through ≥4 to <7 years. Covariates include central nervous system (CNS) anomaly or injury diagnosis codes, including brain anomaly, microcephaly within 45 days of birth, cerebral palsy, epilepsy, or chorioretinitis. We used Cox proportional hazards regression models to estimate hazard ratios and 95% confidence intervals, overall and stratified by sex, birth weight and gestational age outcome (low birth weight or preterm birth), and presence of CNS anomaly or injury.

RESULTS: Among 2 989 659 children, we identified 1044 (3.5 per 10 000) children with cCMV and 74 872 (25.0 per 1000) children with ASD. Of those with cCMV, 49% also had CNS anomaly or injury diagnosis codes. Children with cCMV were more likely to have ASD diagnoses (hazard ratio: 2.5; 95% confidence interval: 2.0–3.2, adjusting for birth year, sex, and region). This association differed by sex and absence of CNS anomaly or injury but not birth outcome.

CONCLUSIONS: Children with (versus without) cCMV diagnoses in Medicaid claims data, most of whom likely had symptomatic cCMV, were more likely to have ASD diagnoses. Future research investigating ASD risk among cohorts identified through universal cCMV screening may help elucidate these observed associations.

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WHAT'S KNOWN ON THIS SUBJECT: Children with congenital cytomegalovirus (cCMV) are at higher risk of neurodevelopmental sequelae. The authors of some small studies have reported a higher prevalence of autism spectrum disorder among children with cCMV than in uninfected children.

WHAT THIS STUDY ADDS: In this analysis of US administrative claims data, children with a diagnosis of cCMV were 2.5 times as likely as children without that diagnosis to also have a diagnosis of autism spectrum disorder.

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Congenital cytomegalovirus (cCMV) is the most common congenital infection in the United States, affecting 1 in every 200 live births.[1,2] Approximately 10% of infants with cCMV are born with symptomatic disease (eg, clinical, laboratory, or brain imaging abnormalities), which is associated with heightened risk of cerebral palsy, epilepsy, intellectual disability, and sensorineural hearing loss.[3,4] Additionally, as many as 15% of children with asymptomatic cCMV infection develop sensorineural hearing loss by age 5 years.[5] Some US states and Canadian provinces have recently begun to implement universal cCMV screening programs, which provide an opportunity for early intervention.[6]

Autism spectrum disorder (ASD) is a developmental disability that manifests as persistent difficulties with social communication and restricted, repetitive behaviors.[7] A 2020 estimate of prevalence across multiple US sites was 27.6 of 1000 8 year olds.[8] Its etiology is likely influenced by diverse genetic and environmental factors, including the intrauterine environment.[9,10] Possible associations between certain prenatal exposures to some viruses and risk of ASD in offspring have been reported.[11–13] It has been hypothesized that infections may contribute to perinatal neuroinflammation, which in turn may alter the expression of genes conferring ASD risk.[9,14]

A cooccurrence of prenatal cytomegalovirus (CMV) infection or cCMV with risk of ASD has been reported in several case series or case-control studies, with ASD ~2 to 3 times more common in children with cCMV and cCMV up to 10 times more common in children with ASD.[15–19,24,25] However, the numbers of children with both cCMV and ASD in these studies were small, including 4 or fewer children with both cCMV and ASD, and differences were not always statistically significant.[19,20] A summary of peer-reviewed publications reporting on the cooccurrence of cCMV and ASD is provided in Supplemental Table 3. Studies have revealed that children born with brain anomalies or disturbances in utero from a variety of causes have a higher risk of ASD because of alterations in fetal central nervous system (CNS) organogenesis and synapse formation.[9] cCMV has likewise been associated with CNS injury and anomalies, due to the virus's neurophilic nature, which enables the disruption of typical fetal brain development.[21–23]

In this study, using a large US administrative claims data set, we assessed the administrative prevalence of ASD diagnosis in young children with and without a cCMV diagnosis, overall and stratified by other conditions associated with increased risk of ASD diagnosis (eg, preterm birth, low birth weight [LBW], and CNS anomaly or injury).[26,27]

METHODS

Data Source

We used 2014 to 2020 administrative data from the Transformed Medicaid Statistical Information System Analytic Files database from the Centers for Medicare and Medicaid Services, which includes information on enrollment, inpatient and outpatient services, and outpatient drug claims. Deidentified data on >100 million Americans, including children and pregnant women, enrolled in state Medicaid or Children's Health Insurance Program (CHIP) plans are included in the database. The use of this database was determined not to require institutional review board approval.

Study Population and Definitions

Our study population consisted of children who were continuously enrolled in Medicaid or CHIP from birth through ≥4 to <7 years. Children with cCMV were identified by the presence of an *International Classification of Diseases, Ninth or Tenth Revisions, Clinical Modification* diagnostic code for cCMV infection (771.1, P35.1) or cytomegaloviral disease (078.5, B25.×) recorded within 45 days of birth, as in our previous studies.[28–30] ASD was defined as 2 or more inpatient or outpatient visits with diagnostic codes for ASD (299.0×, 299.8×, 299.9×, F84.0, F84.5, F84.8, F84.9) ≥6 days apart at a minimum age of 1 year (Supplemental Table 4).[31] The date of the first ASD diagnostic code was used at the time of initial ASD diagnosis.

We assessed the presence of cooccurring diagnoses that have been reported to be associated with cCMV and ASD, including preterm birth, LBW, hearing loss, and CNS anomaly or injury defined as diagnoses of brain anomaly, microcephaly within 45 days of birth, cerebral palsy, epilepsy, or chorioretinitis (Supplemental Table 4).[32–35]

Analysis

We calculated the prevalence and 95% confidence intervals (CIs) of cCMV and ASD by sex, region, birth outcomes (preterm birth and LBW, preterm birth only, LBW only, or neither), the presence of individual or collective CNS anomaly or injury codes, and hearing loss.

We used Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% CIs for ASD in children with and without cCMV, overall, adjusted for birth year, region, and sex. We also conducted stratified analyses by sex, combinations of preterm birth and LBW, and presence of any CNS anomaly or injury to assess potential differences by these characteristics. We elected not to adjust for race and ethnicity in our primary analysis because of missingness of this variable (24%) but included it in a complete-case sensitivity analysis with the 76% of the sample with non-missing values (Supplemental Table 5).

We generated a Kaplan–Meier curve to compare the risk of having a diagnosis of ASD among children with and without cCMV over time. Observation time started at birth. Children who met the ASD case definition were censored when the first ASD diagnostic code was recorded,

and others who did not experience the event, ASD diagnosis, were censored at either death, disenrollment, or the end of the study period follow-up time. For all analyses, we used SAS version 9.3 (SAS Institute Inc, Cary, NC).

RESULTS

A total of 2 989 659 children who were continuously enrolled in Medicaid or CHIP from birth through ≥4 to <7 years were included in this analysis. Overall, we identified 1044 (3.5 per 10 000) children with cCMV and 74 872 (25.0 per 1000) children with ASD (Table 1; Supplemental Fig 2). The administrative prevalence (prevalence of diagnoses) of cCMV was similar by sex but varied by region, with lower prevalence in the West as compared with other regions. The prevalence of diagnosed ASD was higher in males than in females (37.2 vs 12.3 per 1000 children) and in the Northeast as compared with other regions.

The prevalences of both cCMV and ASD diagnoses were higher among children with diagnoses of preterm birth and LBW, LBW only, or preterm birth only, compared with children who were not coded as either preterm birth or LBW (Table 1). The prevalences of CNS anomaly or injury codes and hearing loss were also higher among children diagnosed with cCMV or ASD. For example, hearing loss was 45 times and 5 times as prevalent among children with cCMV and ASD than among those without those diagnoses, respectively.

The Kaplan–Meier curve revealed that children with a cCMV diagnosis were more likely to subsequently have a diagnosis of ASD (Fig 1). Among those who had an ASD diagnosis, the median age at the first claim with an ASD diagnosis was 39 (interquartile range: 31–50) months for children with a cCMV diagnosis and 37 (interquartile range: 30–45) months for children without a cCMV diagnosis. The overall prevalence of ASD diagnosis at the end of the study period was 64.2 (95% CI: 49.3–79.0) per 1000 for children with a cCMV diagnosis and 25.0 (95% CI: 24.9–25.2) per 1000 for children without a cCMV diagnosis (Table 1).

The unadjusted HR for having a diagnosis of ASD was 2.61 (95% CI: 2.03–3.28) comparing children with and without cCMV. The HR adjusted for birth year, region, and sex was 2.54 (95% CI: 1.98–3.19; Table 2). Stratification by sex revealed a much stronger association between cCMV and ASD was observed for females (adjusted HR: 4.65; 95% CI: 3.09–6.59) than for males (adjusted HR: 1.95; 95% CI: 1.40–2.61). Stratification by preterm birth and LBW resulted in slightly lower adjusted HRs (1.79 to 2.15). Stratification by CNS anomaly or injury revealed larger (but not statistically significant) differences with an adjusted HR of an ASD diagnosis among children diagnosed with cCMV of 1.00 (95% CI: 0.74–1.31) in the stratum with CNS anomaly or injury and of 1.60 (95% CI: 0.99–2.40) than in the stratum without any CNS anomaly or injury.

In a sensitivity analysis in which race and ethnicity was included for the subset of cases with non-missing race and ethnicity records, the overall association changed from HR 2.45 to adjusted hazard ratio 2.65 (95% CI: 1.94–3.51; Supplemental Table 5).

DISCUSSION

In this study of administrative claims data for nearly 3 million children enrolled in Medicaid or CHIP, we found that children with a cCMV diagnosis were ∼2.5 times as likely to have an ASD diagnosis compared with children without cCMV. Although there was no association between cCMV and ASD diagnoses among children who had CNS anomaly or injury, the likelihood of an ASD diagnosis among children with cCMV diagnoses was 1.6 times greater for children without cCMV among children without CNS anomaly or injury codes. Although the association between cCMV and ASD diagnosis was not statistically significant for those with or without CNS injury, the HR reduced substantially when stratifying by CNS involvement. These results are consistent with some, but not all, of the association between cCMV and ASD potentially being attributable to brain anomalies caused by cCMV. In addition, when we stratified by preterm birth or LBW, the likelihood of an ASD diagnosis among children with cCMV was approximately twice that of children without cCMV in all strata. Our findings suggest that even among children with cCMV who are not born with brain anomalies or preterm +/− LBW, an increased risk for ASD is still observed.

When our models were stratified by sex, we found the risk of having an ASD diagnosis in females with a cCMV diagnosis was 4.6 times greater than of those without a cCMV diagnosis, and nearly 2 times higher in boys with a cCMV diagnosis. In general, neurodevelopmental disorders, such as ASD, disproportionately affect males, which has been hypothesized to be due to genetic factors (eg, X-linked genetic conditions) and sex hormone involvement.[36,37] It may be that children with cCMV receive more neurodevelopmental surveillance and services at baseline and may be more likely to receive a diagnosis of ASD, whereas ASD is thought to be underdiagnosed in the general population of girls because of more subtle and nonstereotypical presentations.[38,39]

Maternal CMV infection can activate an inflammatory state which may, in turn, impact fetal brain development, thereby increasing the risk of ASD.[13] In the most severely affected pregnancies, the virus may enter and replicate in fetal CNS cells, leading to alterations in embryogenesis.[40,41] These differences in CNS development in utero may, in some cases, be subtle and not manifest as visible pathology on neuroimaging or as medical conditions such as cerebral palsy or epilepsy. The authors of previous studies have suggested that children with symptomatic cCMV may be at particularly elevated risk of ASD.[19,20] We found that the overall prevalence of ASD diagnosis was

TABLE 1 Prevalence of cCMV and ASD Among US Children Enrolled in Medicaid by Sex, Region, and Clinical Characteristics, Medicaid, 2014 to 2020

Characteristics	Total No. of Children	cCMV[a]		ASD[b]	
		n (%)	Prevalence per 10 000 (95% CI)	*n* (%)	Prevalence per 1000 (95% CI)
Total	2 989 659	1044 (100)	3.5 (3.3–3.7)	74 872 (100)	25.0 (24.9–25.2)
Sex					
Female	1 460 253 (49)	477 (46)	3.3 (3.0–3.6)	17 924 (24)	12.3 (12.1–12.5)
Male	1 529 383 (51)	567 (54)	3.7 (3.4–4.0)	56 948 (76)	37.2 (36.9–37.5)
Region					
Northeast	295 765 (10)	105 (10)	3.6 (2.9–4.3)	11 341 (15)	38.3 (37.6–39.1)
North Central	599 916 (20)	234 (22)	3.9 (3.4–4.4)	13 109 (18)	21.9 (21.5–22.2)
South	1 495 492 (50)	564 (54)	3.8 (3.5–4.1)	36 488 (49)	24.4 (24.1–24.7)
West	579 747 (19)	139 (13)	2.4 (2.0–2.8)	13 688 (18)	23.6 (23.2–24.0)
Birth outcomes					
Preterm birth and LBW	131 975 (4)	369 (35)	28.0 (25.2–31.0)	4893 (7)	37.1 (36.1–38.1)
LBW only	51 568 (2)	175 (17)	33.9 (29.3–39.4)	1502 (2)	29.1 (27.7–30.6)
Preterm birth only	122 218 (4)	103 (10)	8.4 (6.9–10.2)	3874 (5)	31.7 (30.7–32.7)
Neither preterm birth nor LBW	2 683 898 (90)	397 (38)	1.5 (1.3–1.6)	64 603 (86)	24.1 (23.9–24.3)
Any CNS anomaly/injury[c]					
Yes	87 430 (3)	511 (49)	58.4 (53.6–63.7)	8150 (11)	93.2 (91.2–95.3)
No	2 902 229 (97)	533 (51)	1.8 (1.7–2.0)	66 722 (89)	23.0 (22.8–23.2)
Brain anomaly					
Yes	37 488 (1)	367 (35)	97.9 (89.6–107.1)	3289 (4)	87.7 (84.8–90.8)
No	2 952 171 (99)	677 (65)	2.3 (1.8–2.1)	71 583 (96)	24.2 (24.1–24.4)
Microcephaly					
Yes	2846 (0)	88 (8)	309.2 (250.9–381.1)	98 (0.1)	34.4 (28.2–42.0)
No	2 986 813 (100)	956 (92)	3.2 (3.0–3.4)	74 774 (99.9)	25.0 (24.9–25.2)
Cerebral palsy					
Yes	13 086 (0)	222 (21)	169.6 (148.7–193.5)	1416 ((2)	108.2 (102.7–114.0)
No	2 976 573 (100)	822 (79)	2.8 (2.6–3.0)	73 456 (98)	24.7 (24.5–24.9)
Epilepsy					
Yes	51 615 (2)	205 (20)	39.7 (34.6–45.5)	5181 (7)	100.4 (97.7–103.1)
No	2 938 044 (98)	839 (80)	2.9 (2.7–3.1)	69 691 (93)	23.7 (23.5–23.9)
Chorioretinitis					
Yes	744 (0)	74 (7)	994.6 (792.0–1249.1)	56 (0)	75.3 (57.9–97.8)
No	2 988 915 (100)	970 (93)	3.2 (3.0–3.5)	74 816 (100)	25.0 (24.9–25.2)
Hearing loss[d]					
Yes	23 686 (1)	367 (35)	154.9 (139.9–171.6)	2819 (4)	119.0 (114.7–123.5)
No	2 965 973 (99)	677 (65)	2.3 (2.1–2.5)	72 053 (96)	24.3 (24.1–24.5)
cCMV					
Yes				67 (0.1)	64.2 (49.3–79.0)
No				74 805 (99.9)	25.0 (24.9–25.2)

[a] Children with cCMV are defined as those with a diagnostic code for cCMV within the first 45 d of birth.
[b] ASD is defined as those with ≥2 inpatient or outpatient diagnostic codes for ASD codes separated by 6 d occurring at age 1 y and older. All diagnostic codes used to identify cCMV, ASD, and birth related risk factors for ASD are included in Supplemental Table 3.
[c] CNS involvement includes brain anomaly, microcephaly, cerebral palsy, epilepsy, or chorioretinitis.
[d] Hearing loss is defined as having ≥3 medical encounters with diagnostic codes for hearing loss. All diagnostic codes used to identify cCMV, ASD, cooccurring conditions, and hearing loss are included in Supplemental Table 3.

higher among children with a cCMV diagnosis versus those without, even when adjusting for potential confounders (birth year, sex, and region) in the Cox proportional hazard model and when stratifying by preterm birth or LBW. Our study does not address the question of whether children with asymptomatic cCMV infection have a higher risk of ASD because it is not possible to reliably identify such children on the basis of administrative data.[42] Our sample of children with cCMV appears heavily weighted toward children with diagnoses for CNS anomaly or injury. Estimates of the overall proportion of CNS diagnoses in a representative cohort of children with cCMV are not available, but the 21% prevalence of cerebral palsy among children with cCMV in our sample is roughly 7 times greater than the prevalence of cerebral palsy in representative samples of children with cCMV[18] and 70 times greater than the population prevalence of cerebral palsy.[43]

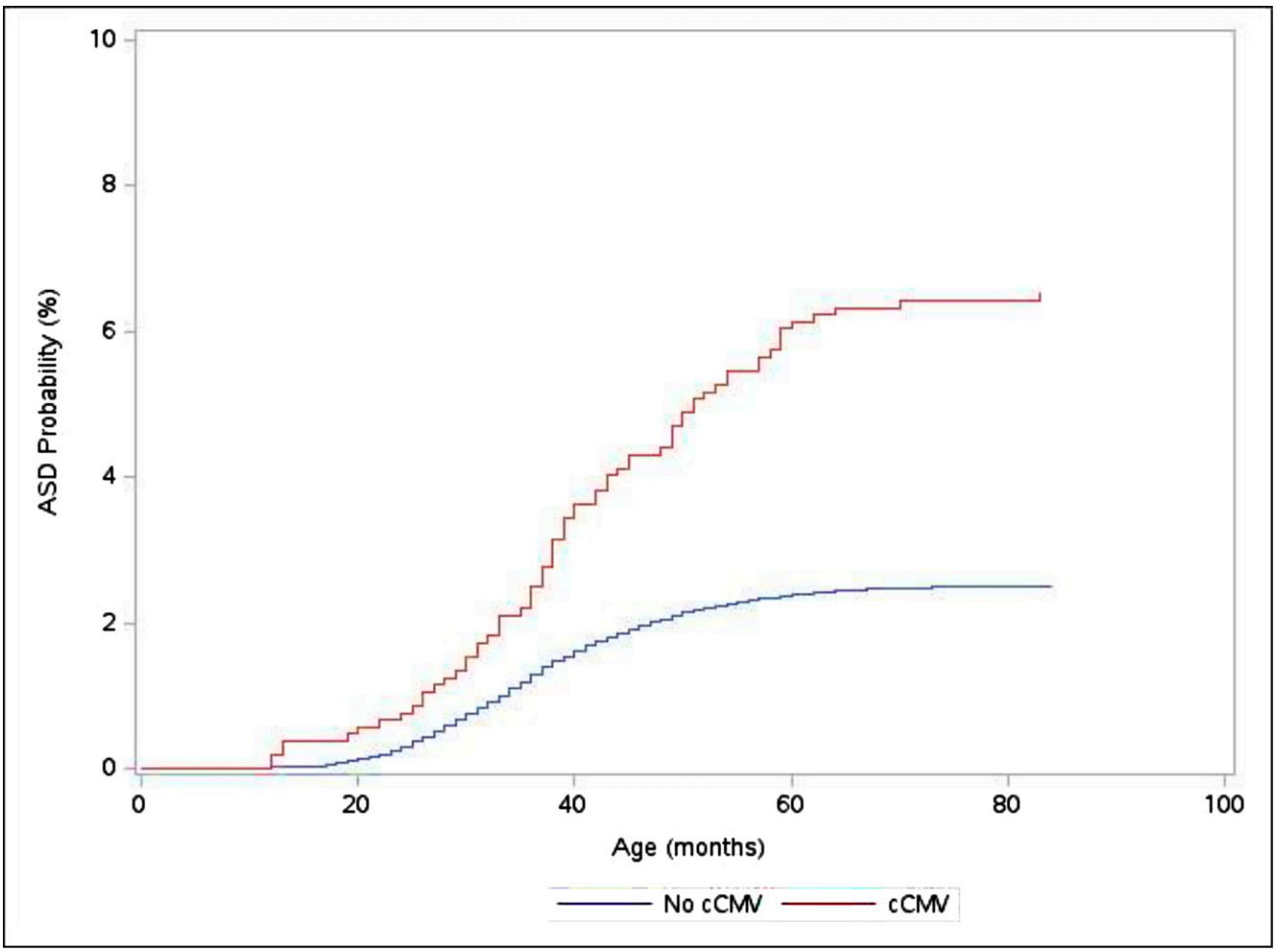

FIGURE 1

Kaplan–Meier curve of ASD diagnosis probability among children with and without cCMV, Medicaid, 2014 to 2020. cCMV was identified by the presence of an International Classification of Diseases, 9th or 10th Revisions, Clinical Modification diagnostic code for cCMV infection (771.1, P35.1) or cytomegaloviral disease (078.5, B25.x) within 45 days of birth. ASD was defined as 2 or more inpatient or outpatient visits with diagnostic codes for ASD (299.0x, 299.8x, 299.9x, F84.0, F84.5, F84.8, F84.9) separated by ≥6 days and occurring at a minimum age of 1 year.

Our study is not without limitations, including inherent limitations of studies using administrative databases, notably the misclassification of conditions resulting from clinical underdiagnosis and inconsistent coding practices.[44,45] Cases identified using these Medicaid administrative data are not generalizable to all infants with cCMV infection. cCMV screening in newborns in the United States is primarily conducted for infants with symptoms suggestive of cCMV, and in places without routine screening for cCMV, most infants with cCMV go undiagnosed.[42,46] Consequently, the administrative prevalence of cCMV in our sample (3.5 per 10 000) was substantially lower than the population prevalence of cCMV infection in large newborn screening studies in the United States (4.5 per 1000).[47] Nondifferential misclassification of both cCMV and ASD status as a result of coding or diagnostic errors could lead to underestimation of HRs toward the null.[2,45] Validation studies for *International Classification of Diseases, Ninth or Tenth Revisions, Clinical Modification* codes for cCMV in administrative data are lacking, whereas administrative ASD diagnoses in North American children have a high positive predictive value for medically diagnosed ASD.[31,48] Differential misclassification, on the other hand, could lead to an overestimation of associations.[45] For example, if children with recognized cCMV are more closely monitored for developmental milestones, they may be more likely to be clinically diagnosed with ASD, as compared with children without cCMV. We had limited ability to adjust for potential confounders, given limitations of Medicaid claims data. The only potential indicator of socioeconomic status of children in the data is eligibility for CHIP versus Medicaid, but we found low continuity of enrollment in CHIP. Finally, although it is possible that requiring at least 4 years of enrollment could introduce selection bias based on factors that influence long-term participation in Medicaid, results were similar using a 1-year enrollment requirement (data not

TABLE 2 Association Between cCMV and ASD, Stratified by Selected Characteristics, Medicaid, 2014 to 2020	
Model	**HR (95% CI)**
All infants	
Unadjusted	2.61 (2.03–3.28)
Adjusted for birth y, region, and sex	2.54 (1.98–3.19)
Strata	
Sex[a]	
Male	1.95 (1.40–2.61)
Female	4.65 (3.09–6.59)
Birth outcomes[b]	
Preterm birth and LBW	2.12 (1.44–2.99)
LBW only	1.79 (0.89–3.14)
Preterm birth only	2.13 (0.91–4.12)
Neither preterm birth nor LBW	2.15 (1.35–3.20)
Any CNS anomaly/injury[b,c]	
Yes	1.00 (0.74–1.31)
No	1.60 (0.99–2.40)

[a] Stratified analyses are adjusted for birth year and region.
[b] Stratified analyses are adjusted for birth year, region, and sex.
[c] CNS anomaly/injury includes cerebral palsy, epilepsy, brain anomaly, microcephaly, or chorioretinitis.

shown). It should also be noted that maternal–infant records were not linked; therefore, this analysis could not include potentially confounding pregnancy factors or maternal characteristics that may be associated with ASD risk.

Given the high costs associated with management of ASD in children and adults,[49] the demonstration of a potentially causal impact of cCMV on risk of ASD could be an important component of the economic impact of cCMV.[50,51] However, the confirmation of a heightened risk of ASD among children with cCMV infection may require data on prospectively monitored cohorts of children in which cCMV infections are identified through universal screening programs, which have recently been initiated in a few jurisdictions.[52] The collection of long-term follow-up data for screened cohorts, including information on ASD and other neurodevelopmental diagnoses that are linked to cCMV screening and diagnostic results, could yield more accurate estimates of the association of cCMV infection with ASD risk, both overall and stratified by the presence of cooccurring conditions. Testing for CMV DNA in stored newborn dried blood spots for samples of children with and without ASD could potentially be informative for research purposes.[53]

Our findings also have clinical implications. Clinicians may want to be proactive in monitoring for early signs of ASD in children with a diagnosis of cCMV, especially those with hearing loss, the risk of which is elevated among both children with cCMV and those with ASD.[54,55] Making a diagnosis of ASD can be challenging in children who are deaf or hard of hearing.[56,57] Although cCMV can only be diagnosed through testing of biological specimens collected in the first few weeks of life,[58] in a few states, clinicians with parental consent might be able to test stored residual dried blood spot specimens for viral DNA for children suspected of having cCMV.[59] As noted above, a finding of cCMV may prompt additional monitoring for developmental outcomes and need for developmental supports.

CONCLUSIONS

In this cohort study, we found that children with Medicaid or CHIP coverage who had a diagnosis of cCMV were more likely to have a diagnosis of ASD than children without a diagnosis of cCMV. Results of the stratified analysis suggest that a diagnosis of ASD is more common among children with cCMV even in the absence of CNS involvement. Future work examining the prevalence of and risk factors for ASD among children with cCMV identified through a universal screening, as well as studies examining the prevalence of CMV identified on newborn dried blood spot specimens in matched cohorts of children with ASD, could better inform our understanding of this association.

ABBREVIATIONS

ASD: autism spectrum disorder
cCMV: congenital cytomegalovirus
CHIP: Children's Health Insurance Program
CI: confidence interval
CMV: cytomegalovirus
CNS: central nervous system
HR: hazard ratio
LBW: low birth weight

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