

A decorative background at the top of the slide features a network diagram with white and light purple nodes connected by thin white lines, set against a gradient background transitioning from orange on the left to dark purple on the right.

# Autism Spectrum Disorder Diagnoses among Insured US Children with Congenital Cytomegalovirus

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# Learning objectives

- **Review the existing literature regarding ASD and cCMV, and why CNS involvement may mediate the relationship between the two.**
- **Discuss the implications of a possible association between cCMV and ASD, and results of this study.**
- **Consider the limitations of using administrative claims data to examine this relationship and discuss the need for future research using universal screening cohorts.**



# Background

- Congenital cytomegalovirus (cCMV) can result in severe outcomes for some infants
- Neurodevelopmental delays and disabilities

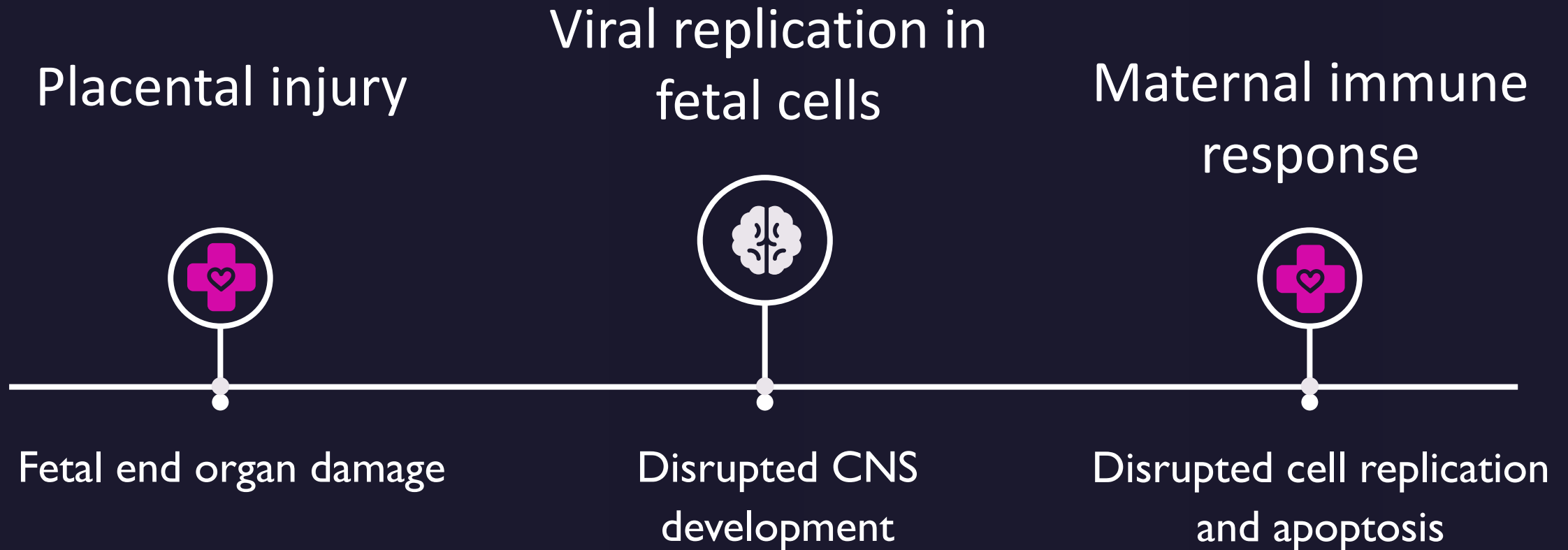


# Autism spectrum disorder

- US Prevalence: 20-30 per 1000 children
- Challenges in social communication, restricted and repetitive behavior or interests
- Risk factors include preterm birth, low birth weight, and central nervous system injury/anomaly



# Congenital infections and fetal injury

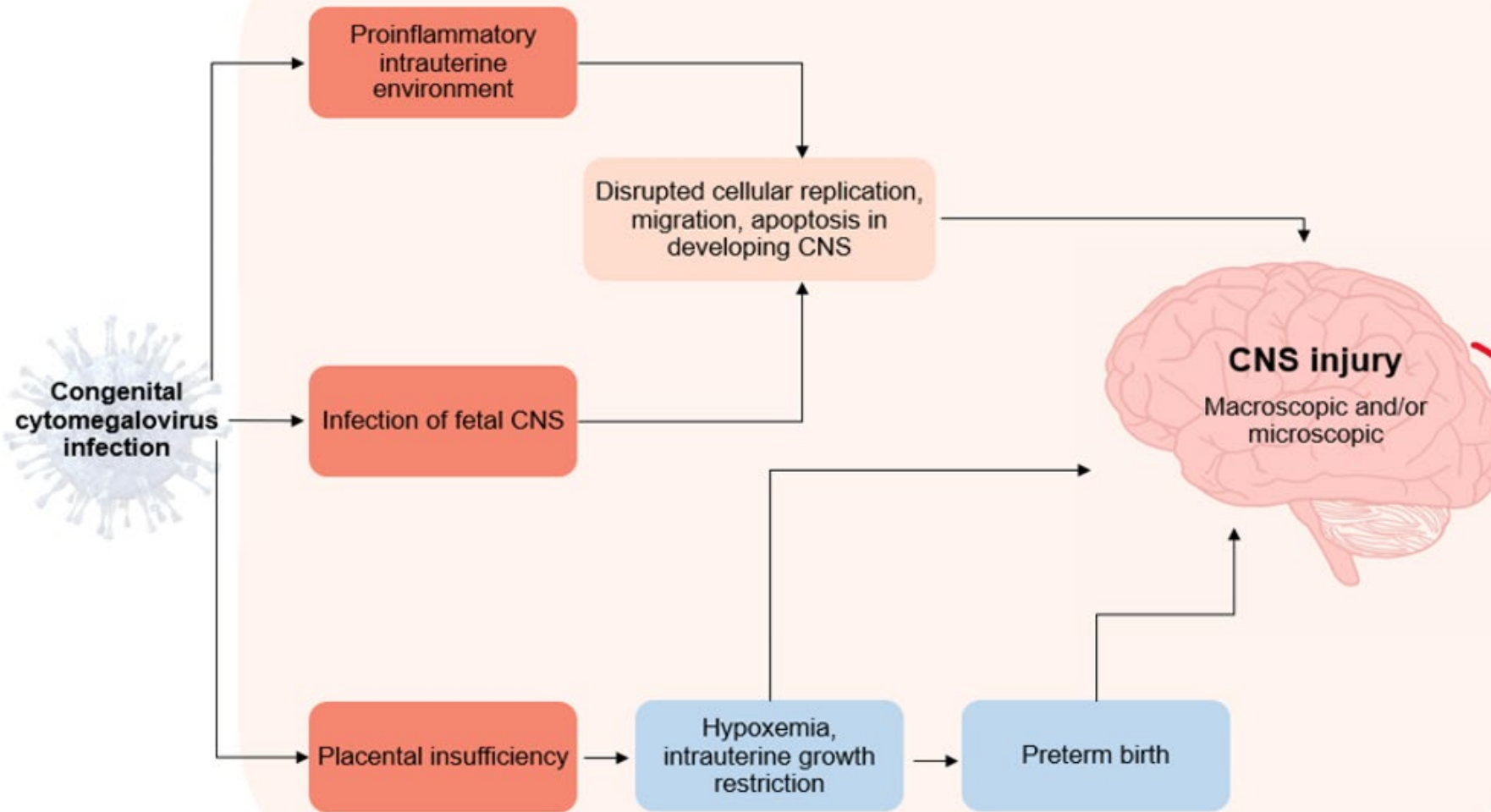


# Congenital CMV and autism

- Many case reports
- Several studies showing increased incidence of ASD in cCMV
  - Biased or small sample sizes
- More common among symptomatic (vs. asymptomatic)
- Causal pathway remains unknown



Severity of effects mediated by fetal gestational age at infection and pre-existing maternal immunity



?

Autism Spectrum Disorder



# Objectives

Assess the risk of ASD diagnosis in children with or without cCMV diagnosis, both overall and stratified by other conditions associated with a higher risk of ASD (e.g., preterm birth, low birth weight, and CNS anomaly/injury)





# Methods


# Data source

- Administrative claims data
- CMS Medicaid data
  - Nationwide data from all US states
  - Inpatient, outpatient and enrollment data
  - Longitudinal data to track patients over time
  - Robust sample size, especially for infants
  - Date of birth available to calculate infant age in days



# Medicaid Datasets and Tables

**2014-2020 CMS The Transformed Medicaid Statistical Information System (T-MSIS) Analytic Files (TAF) Medicaid databases**



## Annual Demographics and Eligibility (DE) File

- Patient ID
- State
- DOB
- Sex
- Race/ethnicity
- Monthly Medicaid Enrollment Days
- Monthly CHIP Enrollment Days
- Death

## Other Services (OT) Claims File

- Patient ID
- Diagnostic codes
- Service dates

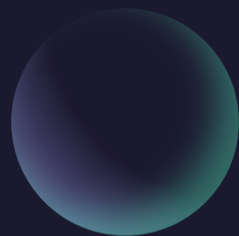
## Inpatient Hospital (IP) Claims File

- Patient ID
- Diagnostic codes
- Service and admission dates
- Patient discharge status



# Study Population

Children enrolled in Medicaid  
continuously since birth  
through  $\geq 4$  to  $< 7$  years



# Study definitions

**Congenital CMV (cCMV):** diagnostic code of cCMV infection or CMV disease within 45 days of birth (IP/OP)

**Autism Spectrum Disorder (ASD):**  $\geq 2$  visits occurring at age 1 or older with a diagnostic code for autism separated by  $\geq 6$  days (IP or OP)

**Preterm birth:** diagnostic code for prematurity (IP)

**Low birth weight:** diagnostic code for LBW (IP)

**CNS anomaly/injury:** diagnostic code for brain anomaly, microcephaly within 45 days (IP only), cerebral palsy, epilepsy, chorioretinitis (IP or OP)

**Hearing loss:**  $\geq 3$  visits with a diagnostic code for hearing loss.



# Analysis

## Prevalence and 95% CI

- By sex, region, birth outcomes, CNS anomaly/injury, and hearing loss

## Directed acyclic graph

- Visualize potential relationship between cCMV and ASD and other variables
- Identified potential confounders

## Kaplan-Meier curve

- Compared the risk of having a diagnosis of ASD among children with and without cCMV over time

## Cox proportional hazard regression model

- Compared HR for ASD in children with and without cCMV, overall, adjusted for sex and region
- Stratified by variables in potential causal pathway, including birth outcomes and CNS anomaly/injury

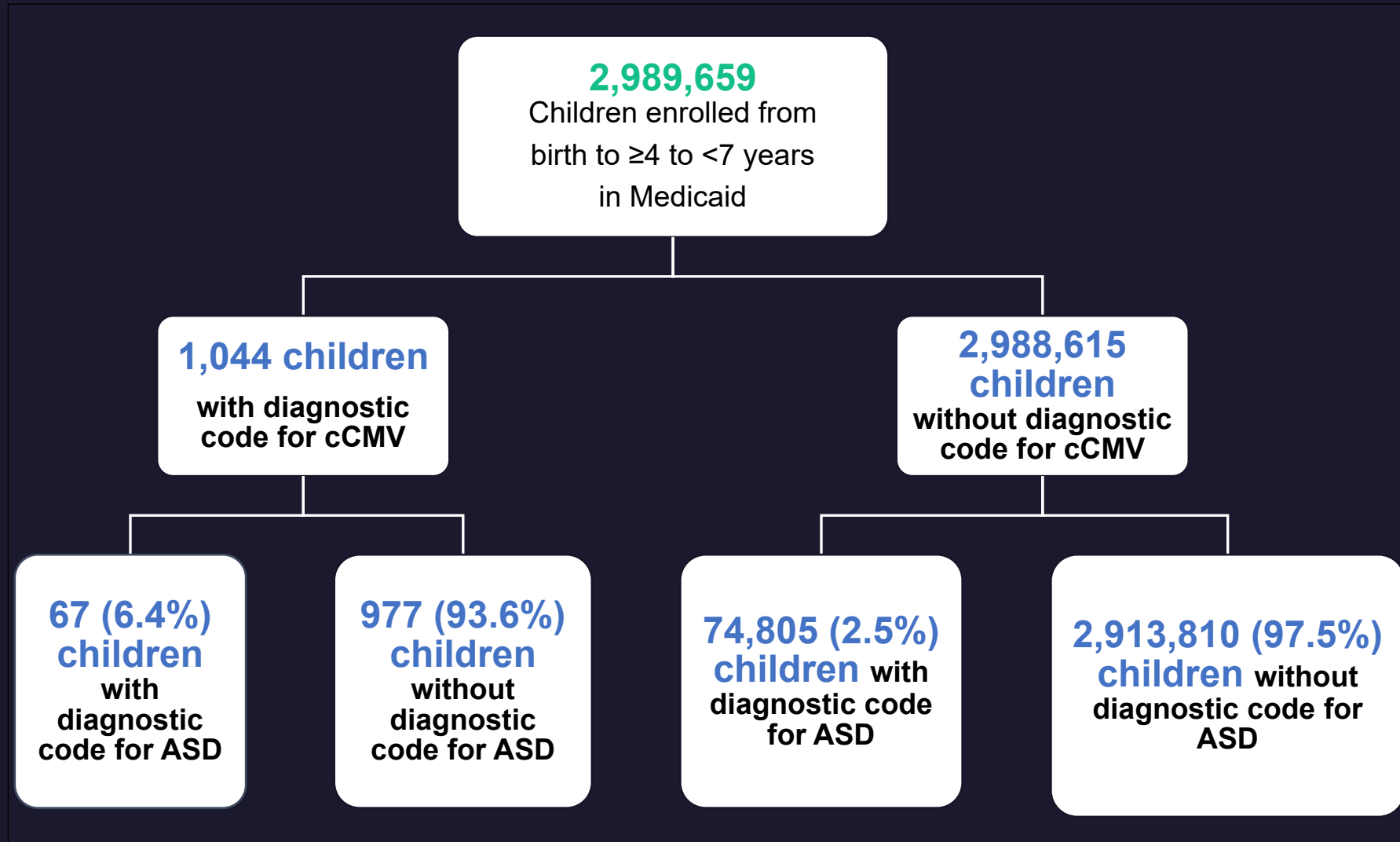




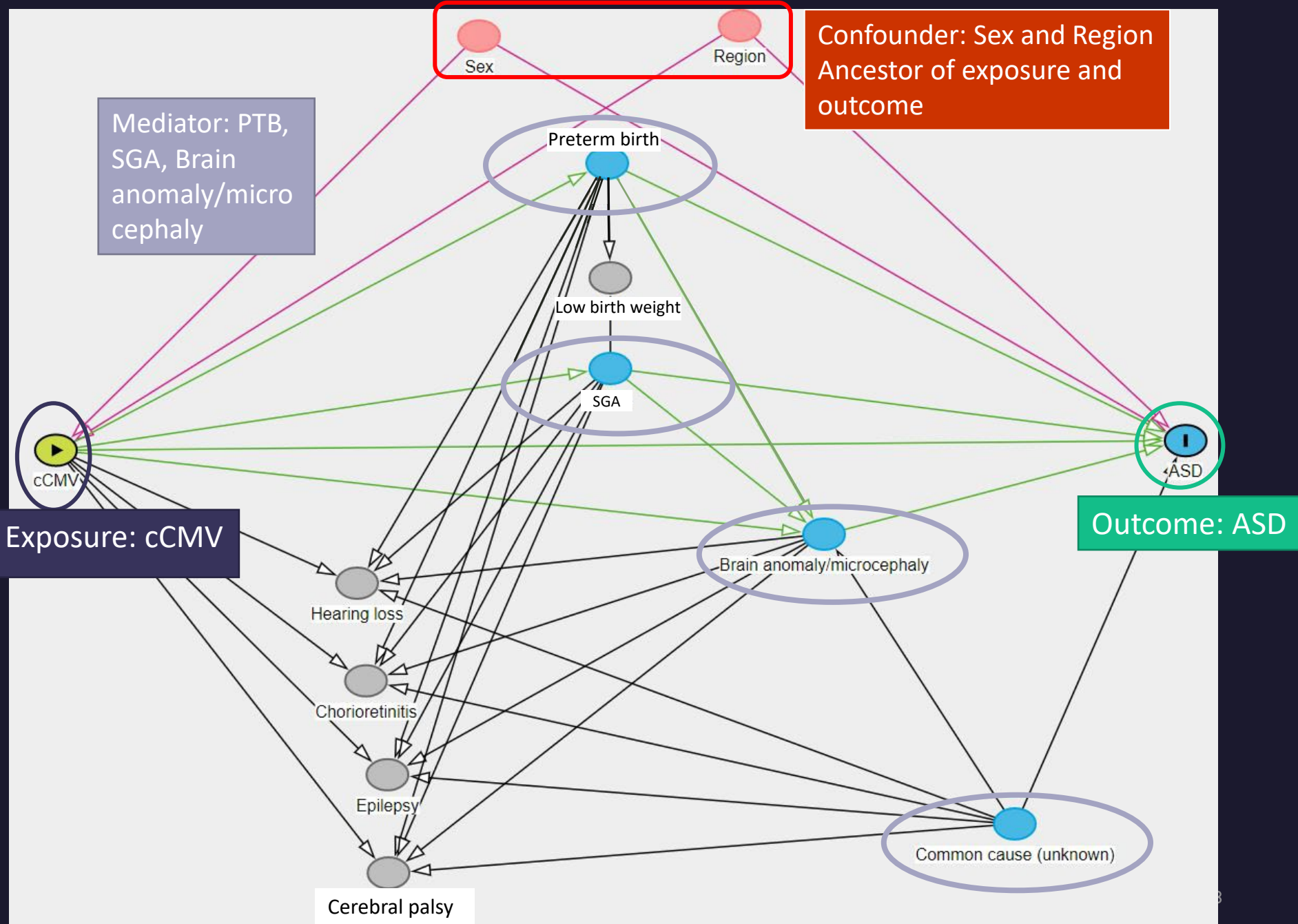
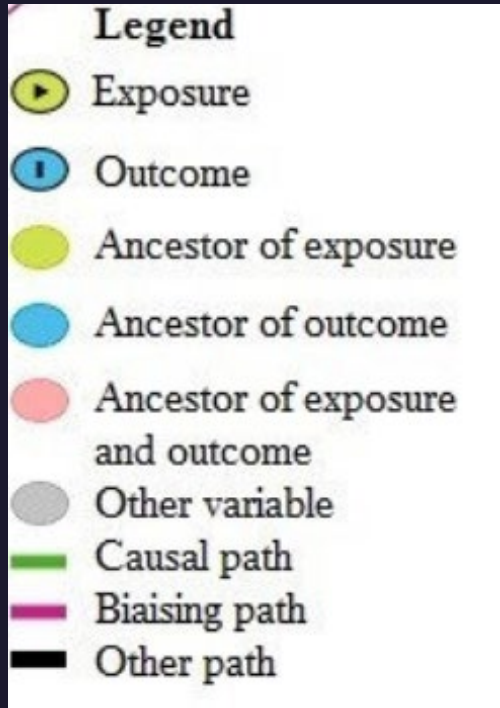
# Results



Study flowchart of children enrolled in Medicaid from birth to  $\geq 4$  to  $< 7$  years with and without diagnostic codes for congenital cytomegalovirus (cCMV) infection and autism spectrum disorder (ASD)



# Directed acyclic graph of cCMV and ASD



# Administrative prevalence of cCMV and ASD among US children enrolled in Medicaid by sex, region and clinical characteristics, CMS Medicaid, 2014–2020

Characteristics	Total number of children	Congenital CMV		Autism Spectrum Disorder	
		n (%)	Administrative Prevalence per 10,000 (95% CI)	n (%)	Administrative Prevalence per 1,000 (95% CI)
<b>Total</b>	2,989,659	1,044 (100)	3.5 (3.3-3.7)	74,872 (100)	25.0 (24.9-25.2)
<b>Sex</b>					
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)
<b>Region</b>					
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)

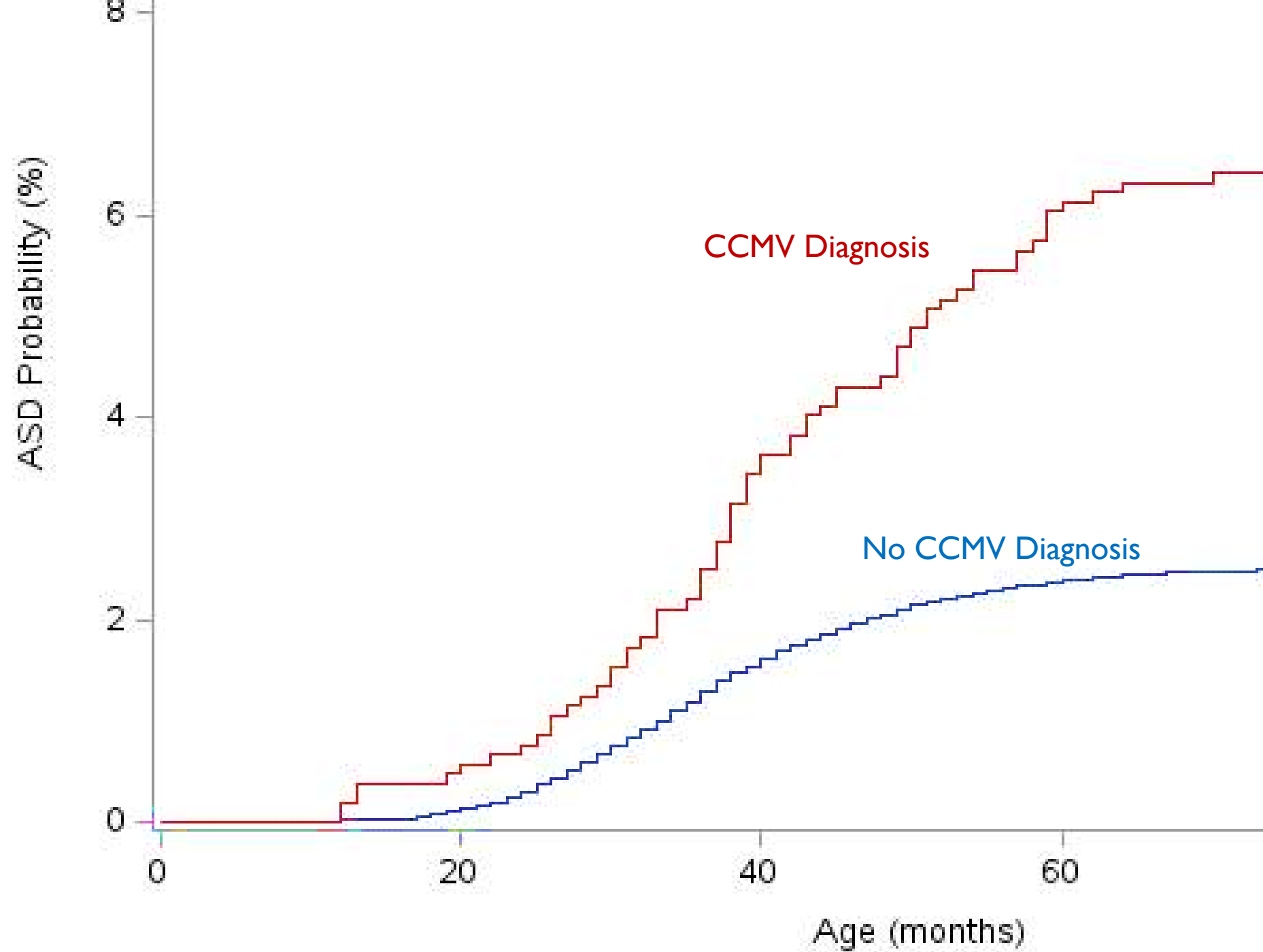
Table 1. Administrative prevalence of cCMV and ASD among US children enrolled in Medicaid by sex, region and clinical characteristics, CMS Medicaid, 2014–2020

Characteristics	Total number of children	Congenital CMV		Autism Spectrum Disorder	
		n (%)	Administrative Prevalence per 10,000 (95% CI)	n (%)	Administrative Prevalence per 1,000 (95% CI)
<b>Birth outcomes</b>					
Preterm and LBW	131,975 (4)	369 (35)	28.0 (25.2-31.0)	4,893 (7)	37.1 (36.1-38.1)
LBW only	51,568 (2)	175 (17)	33.9 (29.3-39.4)	1,502 (2)	29.1 (27.7-30.6)
Preterm only	122,218 (4)	103 (10)	8.4 (6.9-10.2)	3,874 (5)	31.7 (30.7-32.7)
Neither preterm nor LBW	2,683,898 (90)	397 (38)	1.5 (1.3-1.6)	64,603 (86)	24.1 (23.9-24.3)
<b>Any CNS anomaly/injury*</b>					
Yes	87,430 (3)	511 (49)	58.4 (53.6-63.7)	8,150 (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)

\*CNS anomaly/injury includes brain anomaly, microcephaly within 45 days (IP only), cerebral palsy, epilepsy, chorioretinitis



Kaplan-Meier curve of autism spectrum disorder diagnosis probability among children with or without cCMV diagnosis codes, Medicaid, 2014-2020



## Association between cCMV and ASD, stratified by selected characteristics, CMS Medicaid, 2014–2020

Model	Hazard Ratio (95% CI)
<b>All Infants</b>	2.61 (2.03-3.28)
<i>Adjusted for sex and region<sup>a</sup></i>	2.53 (1.97-3.19)
<i>Adjusted for race and ethnicity<sup>a</sup></i>	2.73 (2.00-3.62)
<i>Adjusted for sex, region, race, and ethnicity<sup>a</sup></i>	2.65 (1.94-3.51)

Abbreviations, cCMV, congenital cytomegalovirus; ASD, Autism Spectrum Disorder; LBW, low birth weight; CNS, central nervous system.

<sup>a</sup> Only persons with complete case information were included in the adjusted analyses. For the analysis adjusted by sex and region, only 2,989,633 out of 2,989,659 cases were included in the analysis. For both the analysis adjusted by race and ethnicity, and adjusted by sex, region, race and ethnicity, only 2,271,750 cases were included in the analysis.

<sup>b</sup> Stratified analysis is based on unadjusted data.

<sup>c</sup> CNS anomaly/injury includes cerebral palsy, epilepsy, brain anomaly, microcephaly, or chorioretinitis.

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<b>Strata<sup>b</sup></b>	
<b>Birth outcomes</b>	
Preterm birth and LBW	2.17 (1.47-3.06)
LBW only	1.98 (0.99-3.48)
Preterm birth only	2.19 (0.94-4.24)
Neither preterm birth nor LBW	2.23 (1.40-3.31)
<b>Any CNS anomaly/injury<sup>c</sup></b>	
Yes	0.98 (0.73-1.29)
No	1.66 (1.02-2.47)



# Discussion



# Summary (1)

- Children with cCMV diagnosis were 2.6 times as likely to have an ASD diagnosis compared to children without cCMV
- No association between cCMV and ASD among children who had any CNS anomaly/injury code
- Likelihood of an ASD diagnosis among children with cCMV was 1.7 times higher than for children without cCMV among children without CNS anomaly/injury codes

# Summary (2)

- Some, but not all, of the association of cCMV with ASD may be accounted for by the increased occurrence of CNS involvement among children with symptomatic cCMV
- With some US states implementing screening, it will be important to monitor for neurodevelopmental outcomes, including ASD.
- Future research investigating prevalence and risk factors for ASD among cohorts with universal cCMV screening may help elucidate observations from this study.

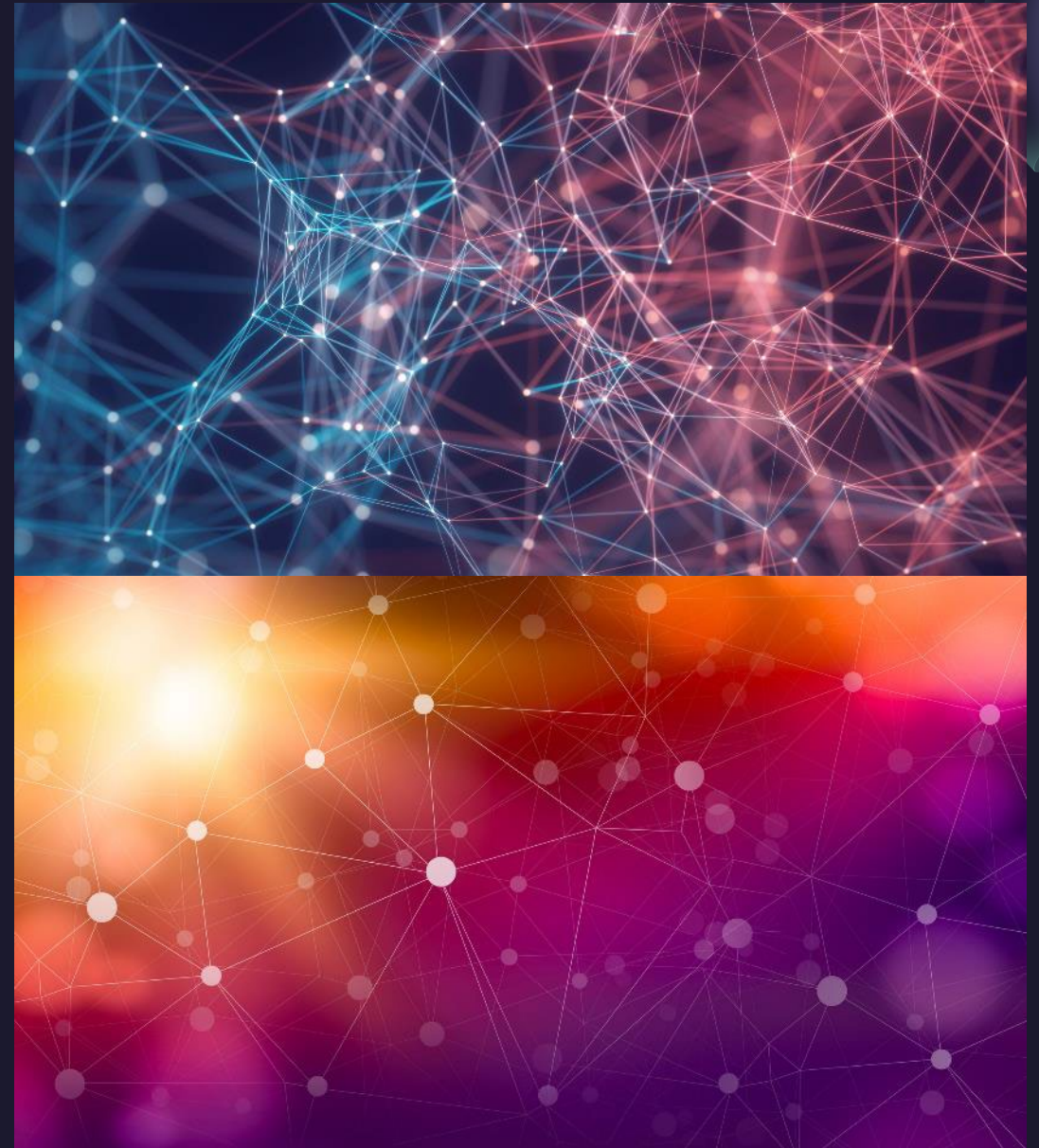
# Limitations

- Administrative data include errors in diagnostic and procedural coding
- Unable to validate with medical record review and no lab test results
- Administrative data only captures diagnosed conditions and may be biased in diagnosed cCMV and ASD cases
- Race/ethnicity groups could be potentially misidentified in the Medicaid administrative enrollment records and information is unproportionally missing in certain states

# Thank You

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IG @DrCMVMom



**Table I. Administrative prevalence of cCMV and ASD among US children enrolled in Medicaid by sex, region and clinical characteristics, CMS Medicaid, 2014–2020**

Characteristics	Total number of children	Congenital CMV		Autism Spectrum Disorder	
		n (%)	Administrative Prevalence per 10,000 (95% CI)	n (%)	Administrative Prevalence per 1,000 (95% CI)
<b>Brain anomaly</b>					
Yes	37,488 (1)	367 (35)	97.9 (89.6-107.1)	3,289 (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)
<b>Microcephaly</b>					
Yes	2,846 (0.1)	88 (8)	309.2 (250.9-381.1)	98 (0.1)	34.4 (28.2-42.0)
No	2,986,813 (99.9)	956 (92)	3.2 (3.0-3.4)	74,774 (99.9)	25.0 (24.9-25.2)
<b>Cerebral palsy</b>					
Yes	13,086 (0)	222 (21)	169.6 (148.7-193.5)	1,416 ((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)
<b>Epilepsy</b>					
Yes	51,615 (2)	205 (20)	39.7 (34.6-45.5)	5,181 (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)
<b>Chorioretinitis</b>					
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)



Table 1. Administrative prevalence of cCMV and ASD among US children enrolled in Medicaid by sex, region and clinical characteristics, CMS Medicaid, 2014–2020

Characteristics	Total number of children	Congenital CMV		Autism Spectrum Disorder	
		n (%)	Administrative Prevalence per 10,000 (95% CI)	n (%)	Administrative Prevalence per 1,000 (95% CI)
<b>Hearing loss</b>					
Yes	23,686 (1)	367 (35)	154.9 (139.9-171.6)	2,819 (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)