HHS Public Access

Author manuscript

Pediatr Res. Author manuscript; available in PMC 2024 July 01.

Published in final edited form as:

Pediatr Res. 2024 January ; 95(2): 418–435. doi:10.1038/s41390-023-02639-6.

Neurodevelopmental Outcomes of Children with Congenital Cytomegalovirus: A Systematic Scoping Review

Megan H. Pesch, MD, MS[a], **Clare S. Lauer, MSW**[a,b], **Jason B. Weinberg, MD, Phd**[c,d]

[a]University of Michigan and CS Mott Children's Hospital, Division of Developmental and Behavioral Pediatrics, Department of Pediatrics, Ann Arbor, Michigan

[b]University of Michigan School of Social Work, Ann Arbor, Michigan

[c]University of Michigan and CS Mott Children's Hospital, Division of Pediatric Infectious Diseases, Department of Pediatrics, Ann Arbor, Michigan

[d]University of Michigan, Department of Microbiology and Immunology, Ann Arbor, Michigan

Abstract

Background: With the emergence of newborn congenital cytomegalovirus (cCMV) screening programs, more infants are being diagnosed and require long term follow-up.

Objectives: To summarize the literature to date on neurodevelopmental outcomes in children with cCMV with attention to study-specific definitions of disease severity (symptomatic vs. asymptomatic).

Methods: This systematic scoping review included studies of children with cCMV (≤ 18 years-old) measuring neurodevelopment in ≥ 1 domain: global, gross motor, fine motor, speech/language, and intellectual/cognitive. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed. PubMed, PsychInfo and Embase databases were searched.

Results: 33 studies met inclusion criteria. Global development most frequently measured (n=21), followed by intellectual/cognitive (n=16) and speech/language (n=8). Most (31/33) studies differentiated children by cCMV severity (symptomatic vs. asymptomatic), definitions of which ranged broadly. 15/21 studies described global development categorically (e.g., normal vs. abnormal). Across studies and domains, children with cCMV generally had equivalent or lower scores (vs. controls or normed measures).

Corresponding author: Megan H. Pesch, Division of Developmental and Behavioral Pediatrics, Department of Pediatrics, University of Michigan, 1540 E. Med Center Drive, Ann Arbor, MI 48019, 734-936-9777, pesch@umich.edu.

Author contributions

All authors participated in the conception, and design of the study, as well as the drafting and critical review of the manuscript for intellectual content. Ms. Lauer conducted the search of the literature. All authors participated in the review of articles for inclusion in the scoping review, as well as data extraction. All authors gave final approval of this version of the manuscript to be published.

Competing interests

Dr. Pesch serves on the Executive Committee of the National CMV Foundation (unpaid) and as a content consultant regarding congenital cytomegalovirus for MedScape/WebMD, neither of which had any input into the conceptualization or creation of this manuscript. Ms. Lauer and Dr. Weinberg have no competing interests to declare.

Conclusions: Variation in definitions of cCMV severity and blunt categorical outcomes may limit the generalizability of findings. Future studies should utilize standardized definitions of disease severity and in-depth measurement and reporting of neurodevelopmental outcomes in children with cCMV.

1. Introduction

Congenital cytomegalovirus infection (cCMV) is a common and often disabling condition, affecting one in every 150 infants globally.[1,2] While cCMV is by no means a new disease, over the last decade rates of diagnosis have climbed, due in part to a growing number of newborn screening initiatives,.[3,4] Increased awareness and recognition of cCMV provides an opportunity for early intervention to mitigate the effects of the virus. As such, there is an increased need to understand the predictors of neurodevelopmental outcomes of children with cCMV to better define prognosis and address needs for anticipatory guidance and early intervention.

There are many possible medical sequelae from cCMV, including intrauterine fetal demise, childhood death, cerebral palsy (CP), vision loss, epilepsy and sensorineural hearing loss.[4] In some cases, there are no apparent sequelae.[5] As such, possible neurodevelopmental outcomes (i.e., the level of skill development affected children attain compared to typical development for age) vary substantially.[5] cCMV severity has been categorized based on presentation at birth, with recent standardization of category definitions in 2017 by expert opinion and consensus guidelines.[6,7] Approximately 10–15% of infants with cCMV are born with *symptomatic disease,* having clinical signs at birth (e.g. petechiae, thrombocytopenia, microcephaly, jaundice, small for gestational age (SGA), seizures), abnormalities on brain imaging, or laboratory abnormalities attributable to infection.[6,8] Of children with symptomatic cCMV, 50–80% will experience long-term medical sequelae. Most infants with cCMV (85–90%) are classified as having *asymptomatic* infection, without overt clinical, radiographic, or laboratory abnormalities. Of note, infants with cCMV who have isolated sensorineural hearing loss (SNHL) are included in the asymptomatic infection category.[6] It has been thought that infants with symptomatic cCMV were at increased risk of for neurodevelopmental delays and disabilities, whereas infants with asymptomatic cCMV were not, apart from sensorineural hearing loss.[8–10] However, recent data suggest that infants with asymptomatic cCMV may be at increased risk for vestibular, gaze stability and balance dysfunction[11] and neurodevelopmental disabilities such as autism spectrum disorders.[12,13] A better understanding and analysis of research examining neurodevelopmental outcomes in children with cCMV is needed.

To our knowledge, there have been no recent comprehensive reviews of neurodevelopmental outcomes in populations including symptomatic and asymptomatic cases. In addition, reviewing neurodevelopmental outcomes within domains of development (e.g., gross motor, fine motor, speech/language and cognitive/intellectual etc.) is important to understanding patterns of strengths and weaknesses. As such, we performed a scoping review of the literature to date addressing neurodevelopmental outcomes in children with cCMV, paying particular attention to outcomes in asymptomatic and symptomatic children and their study-specific definitions.

2. Methods

A scoping review is an approach that is used when previously published studies utilize a of data collection and analysis techniques, or when no prior synthesis has been undertaken on the topic and the researchers will not pursue a quality assessment of the studies.[14] This review will adhere to the protocol outlined by Arksey and O'Malley.[14]

Inclusion and exclusion criteria determined before initiating database searches are shown in Table 1. We focused on studies from peer-reviewed journals presenting primary data from participants with confirmed cCMV and with reported measures of neurodevelopment in at least one of the following domains: global development, gross motor, fine motor, speech/language and/or cognitive/intellectual. For speech and language outcomes, we chose to focus on studies primarily evaluating developmental outcomes, and not those examining hearing status with speech and language as secondary or tertiary outcomes, as there have been several recent reviews examining that subject.[10,15–19]

Initial Medline (PubMed), Psych Info (EBSCO) and Embase (Elsevier) database searches were run on January 8, 2020. Search terms used in the query included neurodevelopmental outcomes, developmental delay, gross motor, fine motor, congenital cytomegalovirus, and cytomegalovirus infection. Search terms were chosen based on an initial small-scale review of the literature in conjunction with consultation from a research librarian and expert on literature reviews. A summary of search terms and limits used for each database is presented in Table 2.

After removal of duplicates, the search produced 1130 studies for screening. Two reviewers independently reviewed 20 titles and abstracts to establish reliability in determining inclusion criteria (kappa = .94). The single disagreement was brought to a third reviewer, and a collective agreement was met. The rest of the abstracts and titles were reviewed for inclusion by a single reviewer, with a second available to discuss unclear studies. The title and abstract review identified 1017 as ineligible based on predetermined inclusion/exclusion criteria, leaving 113 papers for full-text review. Of these studies, 26 were eligible for inclusion, with 87 studies being excluded for reasons shown in Figure 1. Backwards and forwards citation analyses (Scopus) revealed one additional article meeting eligibility criterion. Subsequent search alerts in PubMed identified two additional studies eligible for inclusion in the review. Within the full-text review, an iterative inclusion/exclusion process resulted in exclusion of studies only reporting attention deficit hyperactivity disorder as neurodevelopmental outcomes; studies reporting neurodevelopmental outcomes based on medical diagnoses alone, those that did not use standardized measures, or report which instruments were used.

A follow-up search using identical search terminology was conducted of the same three databases on December 17, 2021, to determine if any additional studies meeting our inclusion criteria had been published. The updated search yielded 4 additional studies meeting inclusion criteria, bringing the total number of included studies to 33. The PRISMA flowchart is shown in Fig 1.

General and specific data about the 33 studies were extracted for comparison and categorization of the studies. A formal review of the quality of evidence and risk of bias was not undertaken. Descriptive statistics for the sample were tabulated. Definitions used in the study are presented in Table 2.

3. Results

3.1 Summary of included studies

A summary of the final corpus of studies is shown in Table 3. Thirty-three studies were included in the scoping review after application of the inclusion and exclusion criteria, representing ~1433 unique cases of cCMV. Overlap in the cohorts of five studies prevented the exact calculation of unique cases of cCMV. Studies from 1974–2021 reported measures of global (n=21), fine motor (n=6), gross motor (n=8), speech/language (n=8) and intellectual/cognitive outcomes (n=16). The ages of children included in the studies ranged from three-weeks to 18-years. Studies reported on cohorts from Africa (1), Asia (8), Middle East (2), United Kingdom (1), Europe (12) and North America (8).

3.2 Definitions of symptomatic and asymptomatic cCMV

Definitions of symptomatic and asymptomatic cCMV ranged widely across studies. All studies that included participants who were specifically noted to have symptomatic disease included some definition of qualifying criteria, although some were not specific (e.g., “clinical findings suggestive of CMV infection”).[20] On the other hand, many studies that included infants with asymptomatic cCMV did not include a clear definition of qualifying criteria for asymptomatic infection (as opposed to symptomatic disease). Explicit definitions of symptomatic disease varied widely and had varying overlap with current consensus definitions of symptomatic disease from International and European groups (Table 4).[6,7] Of note, 18 studies categorized infants with isolated SNHL as having symptomatic disease, whereas according to recent consensus statement and expert definitions such infants would be categorized as having *asymptomatic cCMV with isolated SNHL*.[6,7] Nineteen studies did not evaluate for or did not include the presence of intracranial radiographic abnormalities in criteria for symptomatic disease. Other studies used a broader definition of qualifying symptomatic criteria including isolated jaundice (n=10) (not specifically tied to conjugated hyperbilirubinemia), hypotonia (n=2), seizures (n=4), and/or lethargy (n=2).

3.3 Global developmental outcomes

Global developmental outcomes (Table 5a) were often (14/21) reported categorically, combining medical diagnoses, neurodevelopmental testing, and rehabilitative therapy needs to create categories of “impairment,” sequelae, neurodevelopmental disabilities or “psychomotor development”.

In studies with cohorts comprised primarily of children with symptomatic cCMV, rates of global developmental delay ranged from 43% to 64%. Fukushima et al prospectively followed a cohort of infants with symptomatic cCMV until 18 months (N=21, which included those with isolated hearing loss), finding that half had "typical to moderately delayed development” (DQ (Developmental Quotient) ≥70), and 43% had development in

the significantly delayed range (DQ<70). [21] Children in the DQ<70 group were more likely to have microcephaly or be small for gestational age at birth than children in the DQ ≥ 70 group.[21] In a prospective cohort of infants with symptomatic cCMV evaluated at 18 months, Yamada et al found 65% to have a global developmental quotient in the "impaired" range (DQ ≤70).[22] Kobas et al. reported on global developmental outcomes of infants and young children (ages 6–72 months) born with cCMV (21 of 26 had symptomatic cCMV) using a battery of well-validated measures. Results were reported as "normal" versus "abnormal" global development, which was defined as having a score on at least one subscale or test component <1 SD from the expected mean.[23] Using this definition, 50% of infants with symptomatic cCMV met criteria for "abnormal" global development at ≥ 6 month of age.[23] Finally, Alarcon et al found that 64% of their school aged cohort of children with symptomatic cCMV had "moderate or severe neurodevelopmental disabilities" categorized as the presence of any one of a range of medical conditions, emotional or behavioral problems, or measured global development or cognitive scores below the mean.[24]

Most studies that focused on children with asymptomatic cCMV found no or minimal differences in global developmental outcomes compared to controls or "typical range" scores on standardized normed measures.[25–29] Three studies prospectively or cross-sectionally measured global development in infants and toddlers with cCMV, most of whom had asymptomatic cCMV, and uninfected controls. There were no differences in global developmental scores between cases and controls at between 1 and 2 years-old.[25,27,28,30] Of note, studies by Pathirana, Pearl, and Ivarsson did not include children with SNHL in their definitions of asymptomatic cCMV, and Puhakka et al found no differences in hearing outcomes between cases and controls at 18 months. [20,27,28] Additionally, studies by Pearl and Ivarsson excluded children who developed "neurologic abnormality" in infancy or early childhood, considering them to not be asymptomatic.[28]

Townsend et al, reported no differences in mean global developmental scores in children with cCMV (predominantly asymptomatic, including isolated SNHL) and controls without cCMV at 2 years or 7 years.[26] Zhang et al examined global developmental outcomes in children with asymptomatic cCMV (criteria for determining severity of disease were not described).[29] Lower global DQ scores at 2 and 5 years in children with cCMV compared to controls were largely driven by lower DQ language and verbal IQ scores. Of note, the authors point out that no "deafness" was reported for the cohort, but other details regarding hearing loss were not provided.

Giannattasio et al identified an "impaired neurodevelopmental outcome," defined as the presence of a global developmental /intellectual "impairment" ratio <70, "motor impairment" requiring rehabilitation, epilepsy, behavioral or emotional problems, in 32.6% of children with symptomatic cCMV compared to 8.5% with asymptomatic cCMV.[31] In large cohorts from the UK (176 children with cCMV, 19 of whom had symptomatic cCMV, and 214 controls without cCMV) and Sweden (76 children with cCMV and 62 controls without cCMV), there were no differences in global development scores as measured on the GDS between children with cCMV and controls.[32]

Four studies examined global developmental outcomes in infants with symptomatic or asymptomatic cCMV (as defined by each study) in relation to neuroimaging findings.[33–36] Ancora et al found that global development at 12 months of age in symptomatic infants varied based on cranial imaging, with “poorer” global developmental attainment in those with (versus without) intracranial abnormalities at birth (e.g., calcifications, ventriculomegaly).[33] These findings are echoed by those of Oosterom et al, who also examined global development in relation to intracranial findings in infants with cCMV, finding that “poor neurodevelopmental outcome” (defined as a score of 1 SD below the mean on two measures) was more common in infants with symptomatic cCMV and in those with severe intracranial findings (polymicrogyria, periventricular calcifications, white matter cysts, cerebellar hypoplasia, ventriculomegaly).[34] This study also found no global developmental abnormalities between ages 1–5 years in 70% of children with asymptomatic cCMV (which included those with mild intracranial findings as infants).[34] Giannattasio et al, examined the role of intracranial findings on neuroimaging, in predicting neurodevelopmental outcomes in a cohort of 170 infants with cCMV (112 symptomatic, the definition of which included hearing loss but did not include small for gestational age).[37] “An "impaired neurologic outcome” (defined as the presence of DQ/IG <70, motor delay requiring therapy, epilepsy, behavioral or emotional problems) was observed in 32% (55/170) of the cohort. Using the neuroimaging severity scale developed by Alarcon et al, Giannattasio et al found more severe intracranial findings to be associated with having an “impaired neurologic outcome”.[37]

3.4 Fine motor

Almost all (5/6) of the studies that assessed fine motor skills (Tables 5b) found no difference between children with cCMV and uninfected controls. These study cohorts were predominantly comprised of children with asymptomatic cCMV, definitions of which varied by study. Ivarsson et al examined fine motor skills in a cohort of 35 children with cCMV (30 asymptomatic) and 53 uninfected controls using the Circle Test, which evaluates a child’s hand-eye coordination while using scissors.[28] All children with cCMV and all but one uninfected control passed the Circle Test, with no statistically significant difference in fine motor delay between groups.[28] Puhakka et al evaluated fine motor skills in a cohort of 40 children at age 18 months with cCMV (90% of whom were asymptomatic) and 54 uninfected matched controls; there were no differences between groups in eye-hand coordination score (p=.65).[20] Maes et al assessed the fine motor skills of infants aged 5–9 months in a sample comprised of uninfected controls, infants with asymptomatic cCMV, symptomatic cCMV without hearing loss, symptomatic cCMV with hearing loss, and infants with connexin 26 mutation (SNHL alone).[38] Children with connexin 26 genetic variants were included as comparison group to examine the potential impact of isolated congenital SNHL alone. [38] Grasping and visual motor skills, assessed using the fine motor scale of the Peabody Developmental Motor Scales, were similar in all groups.[38] In an older study of two-year olds with cCMV, Pearl et al found comparable scores on the GSD eye/hand coordination scale in uninfected controls and infants with asymptomatic cCMV (defined as not having any “neurological abnormalities”). [27] Much lower fine motor scores were identified in the five symptomatic children in the sample, two of whom had spastic quadriplegia.[27]

3.5 Gross motor

Eight studies examined gross motor outcomes (Table 5c) in children with cCMV, seven of which used a comparison group of uninfected controls.[20,25,27–29,38,39] Several studies identified in this review reported gross motor outcomes as “delayed milestones” or “mild motor delay” but did not describe a standardized measurement; those studies were therefore not included in this aspect of our review.[31,40–42] The incidence of gross motor developmental delay in children with symptomatic cCMV (as defined by each study) ranged from 30–43%. Alarcon et al examined incidence of CP and corresponding Gross Motor Function Classification System (GMFCS)[43] status in a cohort of 23 surviving children with symptomatic cCMV (defined as including isolated SNHL, but excluding infants with isolated lenticulostriate vasculopathy), aged 19-months to 18-years.[24] Cerebral palsy was reported in 10/23 children, half of whom had a GMFCS score ≥4 indicating a need for assisted or powered wheeled mobility.[24] Maes et al found infants with symptomatic cCMV who also had hearing loss (n=8) to have lower gross motor performance as measured by the Peabody Developmental Motor Scales - 2nd Edition, as compared to uninfected controls (p=.005, 95% CI 4.09–30.41), asymptomatic infants (p=.03, 95% CI 0.72–27.03), as well as those with connexin 26 mutation (p=.016, 95% CI 2.09–28.41).[38]

Studies focusing on children with asymptomatic cCMV (defined by each study) found no difference in gross motor outcomes compared to controls without cCMV.[25,27–29,39] Ivarsson et al and Pathirana et al found no differences in gross motor developmental scores in their respective cohorts of Swedish 1–7 year olds (30/35 asymptomatic) and South African 6–12 month old (42/46 asymptomatic) children with cCMV compared to controls without cCMV.[25,28] Similarly, Zhang et al and Pearl et al each found no difference in gross motor skills at 2 years of age in their respective cohorts of Chinese (definition of asymptomatic cCMV not provided) and UK (asymptomatic defined as not having any ‘neurological abnormalities’) children with asymptomatic cCMV compared to uninfected controls.[27,29]

3.6 Speech and language

Studies of speech and language outcomes (Table 5d) included in this scoping review were limited to the 8 studies in which hearing status was not a primary outcome. Of these studies, most (6/8) found no differences in speech and language outcomes between children with cCMV and control groups, although cohorts were weighted towards or exclusively comprised of children with asymptomatic cCMV.[20,25,44–46] Several of these studies excluded children with SNHL from asymptomatic categorization or did not explicitly describe the hearing status of their cohorts in relation to results.[25,27,47]

In a sample heavily weighted towards children with asymptomatic cCMV, (36 /40 total participants with cCMV) no differences in speech/language outcomes were found between toddlers with cCMV versus matched controls, as measured by Hearing and Language subscale of the Griffiths Scales of Development.[30] Farkas et al examined language outcomes using the Bayley Scale of Infant and Toddler Development-III[48](Language subscale, subgroup aged 11–42 months) or Peabody Picture Vocabular Test (PPVT)[49] (measure of receptive language only, subgroup aged 43–83 months) in a cohort of 20 children with asymptomatic cCMV.[47] In this study, asymptomatic cCMV was defined as not having

visible signs, SNHL, or intracranial abnormalities detected on pre- or postnatal ultrasound, but those with intracranial abnormalities detected on pre- or post-natal magnetic resonance imaging (MRI) were included in the asymptomatic cCMV group.[47] Children with cCMV did not differ from age- and sex-matched controls with regard to language outcomes when scales from each instrument were averaged across the sample *((Z=0.64, SD 0.76 vs. Z*=0.76, SD 0.86), even when stratified by age (and instrument used).[47] Furthermore, no differences were seen when children with cCMV and intracranial abnormalities detected by MRI were compared to those with cCMV and no MRI abnormalities (n=5, *Z*=0.88, SD1.21 versus n=11, *Z*=0.82, SD 0.92).[47] Finally, Kumar et al found no differences in receptive language as measured on the PPVT or collapsed expressive and receptive language scores on the Northwestern Syntax Screening Test[50] when comparing school aged children with asymptomatic cCMV (defined as cCMV that was clinically inapparent at birth), and matched uninfected/postnatally infected children.[44] While SNHL was identified in 4/17 children with cCMV in this study, none was thought to be "*functionally significant*".[44] Of note, language scores in all three groups were very low, with over half of each subgroup scoring in the abnormal/delayed ranges.[44]

Two studies examined speech/language outcomes in children with symptomatic cCMV separately from those with asymptomatic cCMV. Turriziani Colonna et al examined the incidence of "language disorders" (details regarding expressive or receptive language or association with SNHL were not provided) in a cohort of 36 children with cCMV (12 symptomatic).[51] Three children with asymptomatic cCMV and 3 children with symptomatic cCMV (all three of whom also had intracranial abnormalities on MRI) met criteria for a language disorder. [51] Using the Hearing and Language subscale of the Griffiths Developmental Scales, Pearl et al found no differences in scores in 2-year-olds with asymptomatic cCMV (no neurologic involvement, including no SNHL) compared to uninfected controls.[30] Unsurprisingly, significantly lower Hearing and Speech subscale scores were found in the small subgroup of children with symptomatic cCMV (n=5, <.001), 80% of whom had SNHL. Access to assistive hearing devices (e.g., hearing aids and/or cochlear implants) was not described, but such assistance seems unlikely based on limited available amplification technology in the early 1980s.[30]

Results from Zhang et al, stand out from the other studies examining speech and language outcomes in this review, finding lower scores in language development in children with asymptomatic cCMV as compared to uninfected controls.[29] In this prospective matched case-control cohort of children with asymptomatic cCMV (N=49 cCMV and 55 matched controls), children with cCMV (vs. controls) were found to have lower DQ language development scores on the GDS at 2 years respectively ($t = 3.25$, $p = 0.002$) and Verbal IQ scores at 5 years ($t = 3.88$, $p = 0.000$).[29] Of note, children with cCMV were categorized as asymptomatic by review of the medical record, presumably at the time of enrollment, but no further details were provided regarding their criteria for categorization.[29] Furthermore, the extent to which children with cCMV were affected by SNHL and had access to services for hearing loss was reported.

3.7 Intellectual/cognitive development

Of the 16 studies that investigated intellectual/cognitive outcomes in children with cCMV (Table 5e), most used Intelligence Quotient (IQ) as the unit of outcome.[52] Studies that did not differentiate between infants with symptomatic and asymptomatic cCMV largely reported average or typical range cognitive scores on standardized instruments,[40] or scores that did not differ between children with cCMV and controls.[28] Ivarsson et al measured IQ using the Wechsler Intelligence Scale for Children (WISC)[53] in 25 children with cCMV and in 41 controls at 7 years old and found no difference between the groups.[28] Of note, children with cCMV neurological "impairment," including hearing loss prior to age 12 months, were excluded from this study.[28] Alarcon et al followed a cohort of 23 infants with symptomatic cCMV into childhood (mean age 8.7 years ± 5.3 years) using different instruments to measure cognition depending on the age of the child.[54] Just over half (12/23, 52%) of the children met criteria for "cognitive deficit", defined as a defined as a BSID-III cognitive or language score <85 or a global IQ <=70.[54] Of note, the authors included sensorineural hearing loss as a qualifying criterion for symptomatic cCMV but excluded isolated lenticulostriate vasculopathy. Specific domain scores used as criteria for "cognitive deficits" (language, cognition, or global IQ) were not described, nor were results of cognitive testing performed using measures for the older children. Bopanna et al, investigated IQ scores in 36 children in symptomatic cCMV. Only one child had both normal brain imaging and IQ <70, compared to 59% of those who had abnormal findings (OR=11.6, *p=.015*).[55] Noyola et al examined the predictive value of neonatal findings for later IQ in a cohort of children with symptomatic cCMV (N=41; symptomatic cCMV included isolated jaundice or hearing loss, but not isolated intracranial findings).[42] Approximately half (22/41) of this cohort had an IQ in the typical range (≥70).[42] The presence of microcephaly at birth had the highest specificity for having an IQ<70 (100%; 95% CI 84–100), whereas abnormal brain imaging (by CT) had the highest sensitivity (100%; 95% CI 82.3–100).[42] More severe brain abnormalities (assessed with a scoring system)were associated with increased risk of lower IQ.[42] Fowler et al examined IQ at ages 4 and 6 years in a cohort of 197 children with cCMV, 24 of whom had symptomatic disease. Children whose mothers had primary infection during pregnancy were more likely to have an IQ ≤ 70 compared to those whose mothers had recurrent infection during pregnancy (13% versus 0, respectively).[56]

Several studies have found children with asymptomatic cCMV to have IQ scores no different than uninfected controls.[47] Farkas et al studied 21 infants with a prenatal diagnosis of cCMV but normal fetal ultrasounds.[47] All but one was considered asymptomatic at birth, although neuroimaging findings were not included in this definition.[47] No statistically significant differences in cognitive scores were found between children with cCMV and controls without cCMV.[47] Furthermore, no cognitive differences were identified between children with cCMV who did or did not have abnormal fetal brain MRI findings.[47] In a prospective cohort study of children with asymptomatic cCMV and sibling controls, Lopez et al found no statistically significant differences in Full Scale IQ scores (adjusted for maternal education) between children with asymptomatic cCMV with normal hearing and controls at age 5 or 18 years.[46] Of note, children with asymptomatic cCMV *and* SNHL had scores that were on average 7.0 (SE=10) points lower than sibling controls (p<.05) with

normal hearing. That difference was largely attributable to Verbal IQ scores, presumably impacted by their hearing loss.[46]

Zhang et al prospectively followed a cohort of children with asymptomatic cCMV from the Qinba mountain region of China (N=49), measuring cognitive abilities at 6 years of age. Children with cCMV were found to have lower Verbal and Full-Scale IQ scores compared to uninfected controls (M = 82.8 vs 92, p=.015, and M=89.5 vs 85.7, p<.001), although rates of intellectual disability (defined as IQ <70) were similar in both groups (n=4/49 vs. n=1/50).[29]

4. Discussion

Congenital CMV affects 1 in every 150 children globally, or over 16.5 million children worldwide.[1,2] The overall disease burden of cCMV has been challenging to assess,[52] in part due to conflicting reports and valuations of the broad range of potential neurodevelopmental sequelae. Our scoping review identified studies examining neurodevelopmental outcomes in approximately 1433 unique cases of children with cCMV. The exact number of unique cases is unknown given overlap of cohorts in some studies.[21,22,26,28,55,56] We identified 33 studies measuring neurodevelopmental outcomes in at least one of five domains (global, gross motor, fine motor, speech/language, intellectual/cognitive) in children with confirmed cCMV, aged 0–18 years old. Collectively, these studies suggest that neurodevelopmental delays or abnormalities are common among children with cCMV. To our knowledge, this is the first comprehensive review of this topic.

4.1 Key findings

Neurodevelopmental abnormalities were identified in a substantial number of children with cCMV, particularly in children with symptomatic cCMV. Unfortunately, a variety of factors limit drawing more specific conclusions from the results of studies included in our review. Definitions of symptomatic and asymptomatic cCMV varied widely across studies, especially prior to 2017 when expert consensus definitions were published.[6,7] Many studies in this review reported neurodevelopmental outcomes of children with “asymptomatic cCMV” but excluded individuals with isolated SNHL or later-onset neurologic manifestations, who would be considered as having asymptomatic cCMV using current criteria.[6] This could introduce bias when examining the literature in the context of current definitions of symptomatic and asymptomatic cCMV. For instance, if children with SNHL were classified as having symptomatic cCMV in a study examining speech and language outcomes, the asymptomatic cCMV group may have higher scores (less “impairment”) than if those children with SNHL were included in the asymptomatic cCMV group according to current criteria. On the other hand, some studies excluded intracranial abnormalities from their categorization criteria, did not perform neuroimaging, or used neurologic abnormalities with onset later in life as exclusion categorization.[27,28,47] Children with intracranial abnormalities, who today would be considered moderately-to-severely symptomatic, could have been categorized in earlier work as asymptomatic, potentially lowering mean scores for that group. As such, one must exercise caution when examining predictors of neurodevelopmental outcomes in children with cCMV based on severity categories.

Generalization of findings across studies is further complicated by the variation of comparison groups (standardized norms, uninfected controls, or children with differing severity or clinical characteristics of cCMV) and instruments used to measure and report outcomes. While many studies reported using validated instruments that generate standard scores, age equivalents or percentiles, many chose to present results as categories of “impairment”, combining medical diagnoses and sometimes emotional or behavioral difficulties with objective measurements of neurodevelopment. In some studies, children with isolated bilateral hearing loss or a standard score on developmental testing < 1 SD below the mean were grouped in the same “impairment” category as those with cerebral palsy requiring wheeled mobility, intellectual disability and/or epilepsy. These blunt categorizations of neurodevelopmental outcomes are not clinically meaningful for parents and providers of infants and young children with cCMV when assessing prognosis regarding long-term outcomes. Some studies note lower scores on developmental measures for children with cCMV (compared to the norm or controls) without emphasizing that the scores remain in the average range or comment on the possible contribution of hearing loss to neurodevelopmental outcomes.

4.2 Gaps and potential for future research

Altogether, our scoping review highlights large gaps in the literature that limit the generalizability of findings across studies of neurodevelopmental outcomes of children with cCMV and make it difficult to provide detailed, evidence-based clinical guidance for providers and parents. In addition to the gaps mentioned above, we noted few studies that followed children with cCMV into adolescence. Studies included in this review investigated neurodevelopmental outcomes based on presentation at birth without consideration of other contributors to child development. For instance, few studies controlled for maternal educational attainment, insurance status, socioeconomic status, or social determinants of health, all of which may play a role in shaping a child’s neurodevelopmental outcomes pre- and postnatally. Furthermore, no study examined potential impacts of early intervention or access to developmental therapies or interventions such as hearing aids on children’s outcomes. Examining nuanced predictors of neurodevelopmental outcomes, outside of signs and symptoms at birth, may lead to a better understanding of facilitators and barriers to optimized developmental outcomes. Future research is needed to examine the effectiveness of antiviral medication in improving long-term neurodevelopment in infants across the spectrum of cCMV severity.

This scoping review is not without limitations. Only studies published in English were included. While this is frequent practice in scoping reviews, it is possible that relevant studies published in another language were omitted. Furthermore, studies with participants older than 18 years, those focusing on hearing-related speech and language outcomes, and those focusing exclusively on preterm infants with cCMV were excluded from this review. While doing so made our review feasible, it may have introduced an element of inclusion bias. Studies of neurodevelopmental outcomes of preterm infants with cCMV, who inherently have multiple risk factors for neurodevelopmental disabilities, are especially needed. Lastly, studies of children with likely but not confirmed cCMV were excluded, which may have resulted in the omission of some relevant data.

5. Conclusions

cCMV is a common condition that increases risk for neurodevelopmental delay. Efforts to use existing literature to refine predictions about long-term prognosis are hampered by the substantial heterogeneity in definitions of disease severity and outcome measurements. To overcome this barrier, future research should include large multi-center studies of children with cCMV identified through universal screening, rather than convenience cohorts, with repeat measurement of neurodevelopmental over the course of childhood and adolescence. In addition to considering factors present at birth, we encourage investigators in the field to pursue studies of neurodevelopmental outcomes in children with cCMV that focus on how development can be supported postnatally.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors would like to acknowledge Marisa Conte from the Taubman Medical Library at the University of Michigan Medical School for her assistance in performing the scoping review. The authors would also like to acknowledge Seth Dobson from Artful Analytics, LLC and Kathleen Muldoon for their input regarding figures.

Funding.

Megan Pesch is funded by the Eunice Kennedy Shriver National Institute for Child Health and Development, at the National Institutes of Health (5K23HD108278) and the Gerber Foundation.

References

1. Ssentongo P, et al. Congenital cytomegalovirus infection burden and epidemiologic risk factors in countries with universal screening: a systematic review and meta-analysis. JAMA network open 2021;4(8):e2120736–e2120736. [PubMed: 34424308]
2. Fowler KB, et al. Racial and ethnic differences in the prevalence of congenital cytomegalovirus infection. J Pediatr 2018;200:196–201. e191. [PubMed: 29784513]
3. Yassine BB, Hulkower R, Dollard S, Cahill E, Lanzieri T. A legal mapping assessment of cytomegalovirus-related laws in the United States. Journal of Public Health Management and Practice 2022;28(2):E624–E629. [PubMed: 34225306]
4. Pesch MH, Schleiss MR. Emerging concepts in congenital cytomegalovirus. Pediatrics 2022;150(2).
5. Villagomez AN, et al. Neurodevelopmental delay: Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2019;37(52):7623. [PubMed: 31783983]
6. Rawlinson WD, et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. Lancet Infect Dis 2017;17(6):e177–e188. [PubMed: 28291720]
7. Luck SE, et al. Congenital cytomegalovirus: a European expert consensus statement on diagnosis and management. Pediatr Infect Dis J 2017;36(12):1205–1213. [PubMed: 29140947]
8. Pesch MH, Kuboushek K, Weinberg JB, McKee M, Thorne M. Congenital cytomegalovirus infection. BMJ 2021.
9. Pesch MH, Saunders NA, Abdelnabi S. Cytomegalovirus infection in pregnancy: Prevention, presentation, management and neonatal outcomes. J Midwifery Womens Health 2021.
10. Bartlett AW, McMullan B, Rawlinson WD, Palasanthiran P. Hearing and neurodevelopmental outcomes for children with asymptomatic congenital cytomegalovirus infection: A systematic review. Rev Med Virol 2017.

11. Pinninti S, et al. Vestibular, gaze, and balance disorders in asymptomatic congenital cytomegalovirus infection. Pediatrics 2021;147(2).
12. Maeyama K, et al. Congenital Cytomegalovirus Infection in Children with Autism Spectrum Disorder: Systematic Review and Meta-Analysis. J Autism Dev Disord 2018;48(5):1483–1491. [PubMed: 29185167]
13. Slawinski BL, et al. Maternal cytomegalovirus sero-positivity and autism symptoms in children. American Journal of Reproductive Immunology (New York, NY : 1989) 2018;79(5):e12840.
14. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. Int J Soc Res Meth 2005;8(1):19–32.
15. Fletcher KT, et al. The Natural History and Rehabilitative Outcomes of Hearing Loss in Congenital Cytomegalovirus: A Systematic Review. Otol Neurotol 2018;39(7):854–864. [PubMed: 29912824]
16. Xia W, et al. Congenital human cytomegalovirus infection inducing sensorineural hearing loss. Frontiers in Microbiology 2021;12:824.
17. Kraaijenga V, et al. Cochlear implant performance in children deafened by congenital cytomegalovirus—A systematic review. Clin Otolaryngol 2018;43(5):1283–1295. [PubMed: 29768731]
18. Goderis J, et al. Hearing loss and congenital CMV infection: a systematic review. Pediatrics 2014;134(5):972–982. [PubMed: 25349318]
19. Walsh H, Zuwala J, Hunter J, Oh Y. Congenital Cytomegalovirus and Human Immunodeficiency Virus: Effects on Hearing, Speech and Language Development, and Clinical Outcomes in Children. Front Pediatr 2021:1501.
20. Puhakka L, et al. The burden of congenital cytomegalovirus infection: a prospective cohort study of 20 000 infants in Finland. Journal of the Pediatric Infectious Diseases Society 2019;8(3):205–212. [PubMed: 29554325]
21. Fukushima S, et al. Prediction of poor neurological development in patients with symptomatic congenital cytomegalovirus diseases after oral valganciclovir treatment. Brain Dev 2019;41(9):743–750. [PubMed: 31072632]
22. Yamada H, et al. A cohort study of the universal neonatal urine screening for congenital cytomegalovirus infection. Journal of Infection and Chemotherapy 2020;26(8):790–794. [PubMed: 32273174]
23. Kobas M, et al. Clinical characteristics, audiological and neurodevelopmental outcomes of newborns with congenital cytomegalovirus infection. Swiss Med Wkly 2018;148:w14627. [PubMed: 29894555]
24. Alarcon A, et al. Clinical, biochemical, and neuroimaging findings predict long-term neurodevelopmental outcome in symptomatic congenital cytomegalovirus infection. J Pediatr 2013;163(3):828–834.e821. [PubMed: 23587436]
25. Pathirana J, et al. Neurological and growth outcomes in South African children with congenital cytomegalovirus: A cohort study. PloS one 2020;15(9):e0238102. [PubMed: 32941484]
26. Townsend CL, et al. Long-term outcomes of congenital cytomegalovirus infection in Sweden and the United Kingdom. Clin Infect Dis 2013;56(9):1232–1239. [PubMed: 23334811]
27. Pearl KN, Preece PM, Ades A, Peckham CS. Neurodevelopmental assessment after congenital cytomegalovirus infection. Arch Dis Child 1986;61(4):323–326. [PubMed: 2423040]
28. Ivarsson SA, Lernmark B, Svanberg L. Ten-year clinical, developmental, and intellectual follow-up of children with congenital cytomegalovirus infection without neurologic symptoms at one year of age. Pediatrics 1997;99(6):800–803. [PubMed: 9164772]
29. Zhang XW, et al. Physical and intellectual development in children with asymptomatic congenital cytomegalovirus infection: a longitudinal cohort study in Qinba mountain area, China. J Clin Virol 2007;40(3):180–185. [PubMed: 17919973]
30. Puhakka L, et al. The burden of congenital cytomegalovirus infection: A prospective cohort study of 20 000 infants in Finland. J Pediatric Infect Dis Soc 2019;8(3):205–212. [PubMed: 29554325]
31. Giannattasio A, et al. Outcomes of congenital cytomegalovirus disease following maternal primary and non-primary infection. J Clin Virol 2017;96:32–36. [PubMed: 28938230]
32. Griffiths R The abilities of babies: a study in mental measurement 1954.

33. Ancora G, et al. Cranial ultrasound scanning and prediction of outcome in newborns with congenital cytomegalovirus infection. J Pediatr 2007;150(2):157–161. [PubMed: 17236893]
34. Oosterom N, et al. Neuro-imaging findings in infants with congenital cytomegalovirus infection: relation to trimester of infection. Neonatology 2015;107(4):289–296. [PubMed: 25790782]
35. Giannattasio A, et al. Is lenticulostriated vasculopathy an unfavorable prognostic finding in infants with congenital cytomegalovirus infection? J Clin Virol 2017;91:31–35. [PubMed: 28412596]
36. Nishida K, et al. Prediction of neurodevelopmental impairment in congenital cytomegalovirus infection by early postnatal magnetic resonance imaging. Neonatology 2020;117(4):460–466. [PubMed: 32492677]
37. Giannattasio A, et al. Neuroimaging Profiles and Neurodevelopmental Outcome in Infants With Congenital Cytomegalovirus Infection. Pediatr Infect Dis J 2018;37(10):1028–1033. [PubMed: 30222696]
38. Maes L, et al. Comparison of the Motor Performance and Vestibular Function in Infants with a Congenital Cytomegalovirus Infection or a Connexin 26 Mutation: A Preliminary Study. Ear Hear 2017;38(1):e49–e56. [PubMed: 27505220]
39. Shan R, Wang X, Fu P. Growth and development of infants with asymptomatic congenital cytomegalovirus infection. Yonsei medical journal 2009;50(5):667–671. [PubMed: 19881970]
40. Amir J, Atias J, Linder N, Pardo J. Follow-up of infants with congenital cytomegalovirus and normal fetal imaging. Arch Dis Child Fetal Neonatal Ed 2016;101(5):F428–432. [PubMed: 26782597]
41. Numazaki K, Fujikawa T. Chronological changes of incidence and prognosis of children with asymptomatic congenital cytomegalovirus infection in Sapporo, Japan. BMC Infect Dis 2004;4:22.
42. Noyola DE, et al. Early predictors of neurodevelopmental outcome in symptomatic congenital cytomegalovirus infection. J Pediatr 2001;138(3):325–331. [PubMed: 11241037]
43. Palisano RJ, Rosenbaum P, Bartlett D, Livingston MH. Content validity of the expanded and revised Gross Motor Function Classification System. Developmental Medicine & Child Neurology 2008;50(10):744–750. [PubMed: 18834387]
44. Kumar ML, et al. Congenital and postnatally acquired cytomegalovirus infections: long-term follow-up. J Pediatr 1984;104(5):674–679. [PubMed: 6325654]
45. Farkas N, Lev D, Schweiger A, Lerman-Sagie T, Malinger G. The importance of prenatal neuroimaging in prediction of developmental outcome of fetuses infected with cytomegalovirus]. Harefuah 2010;149(1):45–48, 61. [PubMed: 20422841]
46. Lopez AS, et al. Intelligence and Academic Achievement With Asymptomatic Congenital Cytomegalovirus Infection. Pediatrics 2017;140(5).
47. Farkas N, et al. Does normal fetal brain ultrasound predict normal neurodevelopmental outcome in congenital cytomegalovirus infection? Prenat Diagn 2011;31(4):360–366. [PubMed: 21413035]
48. Bayley N Bayley scales of infant and toddler development 2006.
49. Dunn LM, Dunn DM. PPVT-4: Peabody Picture Vocabulary Test. Pearson Assessments; 2007.
50. Lee LL. A screening test for syntax development. Journal of Speech and Hearing Disorders 1970;35(2):103–112. [PubMed: 5442332]
51. Turriziani Colonna A, et al. Long-term clinical, audiological, visual, neurocognitive and behavioral outcome in children with symptomatic and asymptomatic congenital cytomegalovirus infection treated with valganciclovir. Frontiers in Medicine 2020;7:268. [PubMed: 32793607]
52. Grosse SD, Dollard SC, Ortega-Sanchez IR. Economic assessments of the burden of congenital cytomegalovirus infection and the cost-effectiveness of prevention strategies. Semin Perinatol 2021:151393. [PubMed: 33551180]
53. Wechsler D, Kodama H. Wechsler intelligence scale for children Vol 1: Psychological corporation New York; 1949.
54. Alarcon A, Martinez-Biarge M, Cabanas F, Quero J, Garcia-Alix A. A Prognostic Neonatal Neuroimaging Scale for Symptomatic Congenital Cytomegalovirus Infection. Neonatology 2016;110(4):277–285. [PubMed: 27344149]

55. Boppana SB, et al. Neuroradiographic findings in the newborn period and long-term outcome in children with symptomatic congenital cytomegalovirus infection. Pediatrics 1997;99(3):409–414. [PubMed: 9041297]
56. Fowler KB, et al. The outcome of congenital cytomegalovirus infection in relation to maternal antibody status. N Engl J Med 1992;326(10):663–667. [PubMed: 1310525]
57. Coscia A, et al. Risk of symptomatic infection after non-primary congenital cytomegalovirus infection. Microorganisms 2020;8(5):786. [PubMed: 32466137]
58. Grue J The social meaning of disability: a reflection on categorisation, stigma and identity. Sociology of Health & Illness 2016;38(6):957–964. [PubMed: 27363597]
59. American Psychiatric Association. Desk reference to the diagnostic criteria from DSM-5 (R) American Psychiatric Association Publishing.; 2013.
60. Green SE. "What do you mean 'what's wrong with her?'": Stigma and the lives of families of children with disabilities. Social science & medicine 2003;57(8):1361–1374. [PubMed: 12927467]
61. Leyder M, et al. Primary maternal cytomegalovirus infections: accuracy of fetal ultrasound for predicting sequelae in offspring. Am J Obstet Gynecol 2016;215(5):638.e631–638.e638.
62. Lucignani G, et al. A new MRI severity score to predict long-term adverse neurologic outcomes in children with congenital Cytomegalovirus infection. J Matern Fetal Neonatal Med 2019:1–8.
63. Tanimura K, et al. Immunoglobulin fetal therapy and neonatal therapy with antiviral drugs improve neurological outcome of infants with symptomatic congenital cytomegalovirus infection. Journal of Reproductive Immunology 2021;143:103263. [PubMed: 33422744]
64. Reynolds DW, et al. Inapparent congenital cytomegalovirus infection with elevated cord IgM levels. Casual relation with auditory and mental deficiency. N Engl J Med 1974;290(6):291–296. [PubMed: 4358447]
65. Saigal S, Lunyk O, Larke RP, Chernesky MA. The outcome in children with congenital cytomegalovirus infection. A longitudinal follow-up study. Am J Dis Child 1982;136(10):896–901. [PubMed: 6181675]
66. Suzuki Y, Toribe Y, Mogami Y, Yanagihara K, Nishikawa M. Epilepsy in patients with congenital cytomegalovirus infection. Brain and Development 2008;30(6):420–424. [PubMed: 18215482]
67. Woolger C Wechsler intelligence scale for children-(WISC-III). Understanding psychological assessment 2001:219–233.
68. Flanagan D, Alfonso V, Mascolo J, Hale J. The Wechsler Intelligence Scale for Children - Fourth Edition in Neuropsychological Practice In:2010.
69. Fenson L, Marchman VA, Thal D. MacArthur-Bates Communicative Development Inventories: User's Guide and Technical Manual Paul H. Brookes Publishing Company; 2007.
70. Josse D Brunet-Lézine Révisé: Echelle de développement psychomoteur de la première enfance. Éd. et applications psychologiques; 1997.
71. Green E, et al. Griffiths Scales of Child Development 3rd Edition; Part 2: Administration and scoring 2016.
72. Ikuzawa M, Matsushita Y, Nakase A. Kyoto Scale of Psychological Development 2001 Kyoto, Japan: Kyoto International Social Welfare Exchange Centre; 2002.
73. Griffith R, Luiz D, Infant AfRi, Development C. Griffiths Mental Development Scales, Extended Revised: GMDS-ER; Two to Eight Years. Hogrefe, the Test People; 2006.
74. Bayley N Bayley Scales of Infant Development, Second Edition: Manual San Antonio, TX: The Psychological Corporation.; 1993.
75. Wechsler D Manual for the Wechsler intelligence scale for children-Revised Psychological Corporation; 1974.
76. Wechsler D Manual for the Wechsler Preschool and Primary Scale of Intelligence-Revised San Antonio: Psychological Corporation.; 1989.
77. Wechsler D Manual for the Wechsler preschool and primary scale of intelligence Psychological Corporation; 1967.
78. Woltmann AG. The Bender Visual-Motor Gestalt Test 1950.

79. Gesell A The mental growth of the pre-school child: A psychological outline of normal development from birth to the sixth year, including a system of development diagnosis Macmillan; 1925.
80. Adams W, Sheslow D. Wide range assessment of visual motor ability (WRAVMA) Wilmington, DE: Wide Range. 1995.
81. Folio MR, Fewell RR. PDMS-2: Peabody Developmental Motor Scales. Pro-ed; 2000.
82. Stott D A general test of motor impairment for children. Developmental Medicine & Child Neurology 1966;8(5):523–531. [PubMed: 5972873]
83. Marini A, Marotta L, Bulgheroni S, Fabbro F. Batteria per la Valutazione del Linguaggio in Bambini dai 4 ai 12 anni Firenze, Italy: Giunti OS. 2015.
84. Wechsler D WPPSI-R: Wechsler preschool and primary scale of intelligence-revised Psychological Corporation San Antonio; 1989.
85. Ammons RB, Ammons C. The quick test (QT): provisional manual. Psychological Reports 1962;11(1):111–161.
86. Wechsler D Wechsler Abbreviated Scale of Intelligence 1999.
87. Dunn LM, Dunn LM. Peabody Picture Vocabulary Yest-Revised American guidance service, Incorporated; 1981.
88. Brownell Martin NA. Expressive One-Word Picture Vocabulary Test -- 4 2011.
89. Wechsler D Wechsler Preschool and Primary Scale of Intelligence–Third Edition (WPPSI-III). In: Pearson Assessment; 2009.
90. Bayley N Manual for the Bayley scales of Infant development Psychological Corporation; 1969.
91. Alpern G, Boll T, Shearer M. Developmental profile II. J Read 1980;18:287–291.
92. Roid GH, Miller LJ. Leiter International Performance Scale-Revised (Leiter-R) Wood Dale, IL: Stoelting. 1997;10.
93. Kaufman A, Kaufman N. Kaufman Assessment Battery for Children Interpretive Manual Circle Pines, MN: American Guidance Service; 1983.
94. Terman LM, Merrill MA. Stanford-Binet intelligence scale: Manual for the third revision, form lM 1960.

Impact:

- Neurodevelopmental delays are common among children with cCMV, although gaps in the literature to have made quantification of such delays challenging
- Variation in definitions of *asymptomatic* and *symptomatic* cCMV as well as the use of categorical outcomes of neurodevelopment (e.g., normal vs. abnormal) limits the generalizability and clinical utility of findings

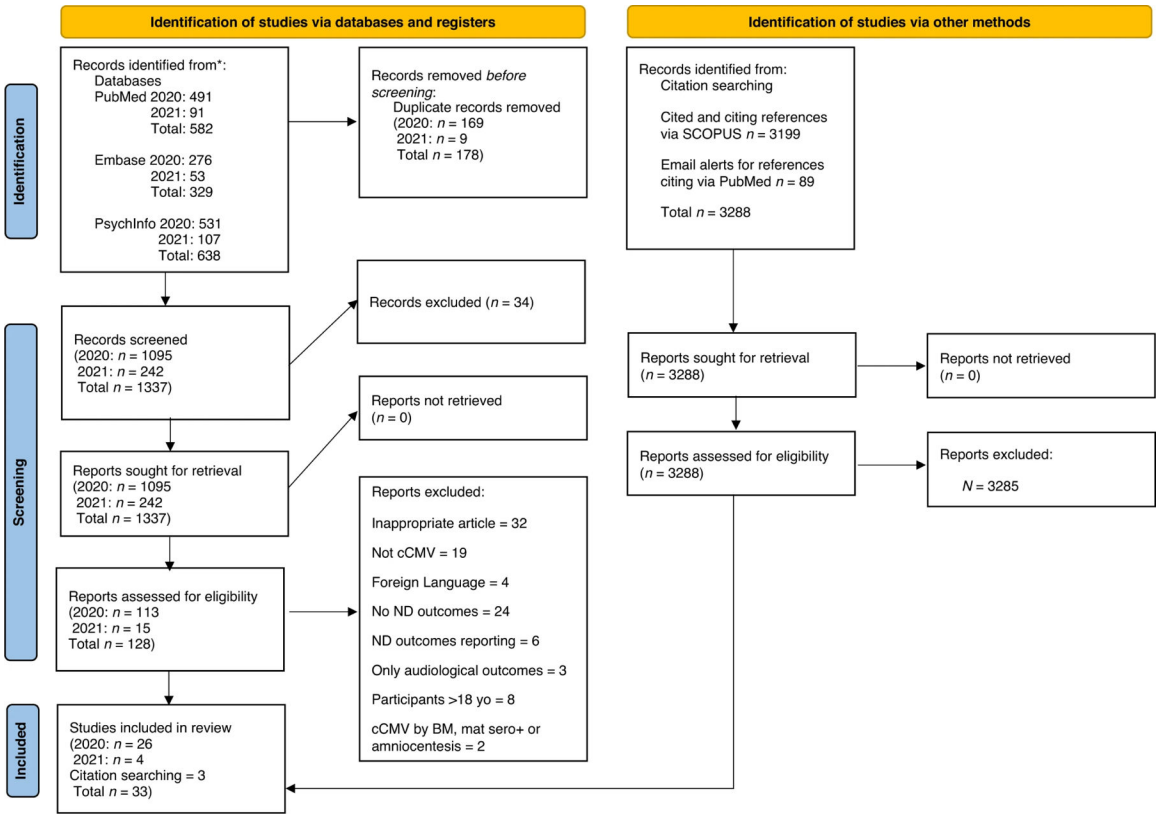

Figure 1:
PRISMA flowchart of the systematic scoping review process

Table 1.

Inclusion and exclusion criteria for the scoping review

Inclusion criteria
Peer-reviewed studies published in journals reporting primary data on neurodevelopmental outcomes
Participants must be human (no animal studies), aged ≤18 years old at the time of neurodevelopmental measurement with congenital cytomegalovirus
Congenital cytomegalovirus status must be confirmed using polymerase chain reaction, or nucleic acid amplification test, or viral culture of the newborn dried blood spot, dried umbilical cord, amniotic fluid (via amniocentesis in utero), or newborn urine, saliva or serum (serum, urine or saliva must be collected within 21 days of birth).
Studies from any country or region included that are published in English language
Studies measuring neurodevelopmental outcomes using standardized instruments (including questionnaires) in at least one of the following domains: Global, gross motor, fine motor, speech/language, and cognitive/intellectual development.
Exclusion criteria
Review papers, conference abstracts, case series and case studies, or published studies with less than 15 participants with congenital CMV
Non-English language studies
Studies using vague descriptions of how congenital cytomegalovirus confirmed, such as ‘a child excreted CMV’, those using post-natal testing without confirming the infection was congenital, or those reliant on maternal or infant serologies alone for diagnosis
Studies reporting on outcomes of participants past 18 years of age
Studies reporting neurodevelopmental outcomes based on medical diagnoses alone without use of standardized measures, or studies that do not report instrument(s) used to assess neurodevelopmental outcomes
Studies exclusively with preterm infant participants
Studies whose primary focus was audiologic outcomes

Table 2.

Definitions of key terminology used in the systematic scoping review

Terminology	Definition
Congenital CMV infection	A fetal infection with cytomegalovirus that was acquired in-utero.[6]
Symptomatic cCMV disease *	An infant born with cCMV and clinically apparent sequelae by physical exam, fundoscopic exam, imaging and/or laboratory studies, but not including infants with isolated SNHL. [6]
Asymptomatic cCMV infection *	An infant born with cCMV but with no clinically apparent sequelae by physical exam, fundoscopic exam, imaging and/or laboratory studies. Infants with isolated SNHL and no other findings are included. [6]
Neurodevelopmental outcome:	Level of skill development in infants or children as compared to typical development for age, most often reported in areas of functioning (e.g., gross motor, language, cognitive etc.).[5]
Neurodevelopmental delay	Level of skill development in infants or children which is greater than two standard deviations lower than typical development for age. [5]
Neurodevelopmental domain	Developmental areas underlying functional or observable performance and abilities of a child.[5] For the present review, in line with the definition of neurodevelopmental outcome/delay, the domains of fine motor, gross motor, speech/language and cognitive/intellectual will be considered.[5] Each domain of development has its own trajectory, which may be influenced by other domains of development. As such, global development, a measure of overall development is also included. [5]

A note on respectful and non-stigmatizing terminology regarding neurodevelopmental delays. As developmental delays and disabilities are conditions that can carry social stigma, the original medical term can in itself lose its neutral tone and become stigmatizing.[58,60] Herein, we have updated terminology referring to developmental disabilities or delays that, while at the time of the may have been considered neutral (e.g., cognitive impairment or mental retardation), are today considered derogatory. Specifically, we use the terms *intellectual/cognitive delay or disability* in line with changes in US federal law, as well as the Diagnostic and Statistical Manual of Mental Disorders-V when applicable.[59] Other terms such as “impaired neurodevelopmental outcome” or “cognitive deficit” that are used by studies to identify categories of neurodevelopmental delay as defined in that study, which do not map onto accepted definitions of intellectual disability or delay, are included in the results of this review but noted in quotes, to highlight that these terms are study specific.

* Differing definitions of what criteria constitute symptomatic or asymptomatic cCMV used by individual studies are presented below and are contrasted to the expert consensus definitions for clarity throughout the manuscript.[6,7]

Table 3.

Overview of studies of developmental outcomes infants and children with congenital cytomegalovirus infection included in the narrative review

Study	Country	Study design	N and participants*	Age at neurodevelopmental assessment	Developmental domain(s) assessed
Alaron et al, 2013[24] **	Spain	Mixed prospective and retrospective cohort	23 surviving children with symptomatic cCMV care for at a single center	Mean age 8.7 years ± 5.3 years (range 19 months to 18 years)	Global Gross motor Cognitive
Amir et al, 2016[40]	Israel	Retrospective cohort	27 children with cCMV (severity not stated), recruited from a cohort of 98 children with cCMV (60 symptomatic)	Median age at follow-up 32 months (range 12–83 months)	Cognitive
Ancora et al., 2007[33]	USA	Prospective cohort	57 neonates with cCMV (20 symptomatic, 37 asymptomatic)	Development assessed at 6, 12, and 24 months. Mean age at last follow-up visit was 42.3 months, SD 11.3 months	Global
Boppana et al, 1997[55] **	USA	Prospective cohort	36 surviving children with cCMV and psychometric testing (all symptomatic), cohort overlaps with Fowler et al[56]	Median 35 months (range 1–143.5 months) for the referred group and 29.2 months (range 0.7–98 months) for the NBS group	Cognitive
Turriziani Colonna et al, 2020[51] **	Italy	Retrospective cohort	36 surviving children with cCMV (12 symptomatic) treated with valganciclovir	Mean age at follow-up was 4.23 years ± 1.5 years	Speech/language Cognitive
Coscia et al., 2020[57]	Italy	Retrospective cohort	91 children with cCMV (37 symptomatic) cared for in the neonatal intensive care unit at a single hospital over a 13-year period	Testing performed at 12 (all infants) and 24 months (symptomatic only)	Global
Farkas et al, 2011[47]	Israel	Retrospective matched case-control cohort	21 children with cCMV (1 symptomatic), and 21 age- and sex-matched controls	Mean age 34.4 ± 16.7 months	Fine motor Speech/ language Cognitive
Fowler et al, 1992[56]	USA	Prospective cohort	197 children with cCMV (123 symptomatic), 100 included in analysis of developmental outcomes	Mean age 4.7 years	Cognitive
Fukushima et a, 2019[21]	Japan	Prospective cohort	21 infants surviving infants with cCMV (all symptomatic) who received 6 weeks or 6 months of oral valganciclovir	Testing performed ~ 18 months corrected gestational age	Global
Giannattasio et al, 2017[31]	Italy	Prospective cohort	158 children with cCMV (88 symptomatic) – cohort overlaps with Giannattasio et al, 2018[37]	Mean age at last observation 3.7 ±2.6 years	Global
Giannattasio et al, 2018[33] **	Italy	Prospective cohort	170 infants with cCMV (112 symptomatic), cohort overlap with Giannattasio et al, 2017[31]	Mean age at last observation 4.7 ± 2.5 years	Global
Ivarsson et al, 1997[28]	Sweden	Prospective case-control cohort	35 infants with cCMV (5 symptomatic) without SNHL or apparent “neurologic disturbances”, and 53 controls	Median age first follow-up was 89 weeks, range 81–107 weeks; Median age at second follow-up was 86 months, range 82–90 months	Global Fine motor Gross motor Cognitive
Kobas et al, 2018[23]	Switzerl and	Retrospective cohort	26 infants with cCMV (21 symptomatic) with measurements of development available cared for at a single center	Range 6–72 months	Global

Study	Country	Study design	N and participants*	Age at neurodevelopmental assessment	Developmental domain(s) assessed
Kumar et al, 1984[44]	USA	Retrospective case-control cohort	17 children with asymptomatic cCMV, 10 children with postnatal CMV infections and 21 uninfected controls	Mean age 7.6 years, range 4.5–10.5 years	Speech/language Cognitive
Leyder et al, 2016[61] *	Belgium	Prospective cohort	35 live-born infants with cCMV (from a cohort of 67 cCMV infected fetuses)	Not reported	Global
Lopez et al, 2017[46]	USA	Prospective case-control cohort	89 children with asymptomatic cCMV (11 with SNHL), and 40 unmatched controls	Median age at last assessment was 13 years (expressive vocabulary) and 17 years (all other measures)	Speech/language Cognitive
Lucignani et al, 2019[62]	Italy	Retrospective cohort	44 children with cCMV (27 symptomatic) who had a prior brain MRI on record	Testing performed at child age ≥24 months	Global
Maes et al, 2017[38]	Belgium	Prospective case-control cohort	24 infants with cCMV (16 symptomatic, 8 of whom had SNHL), 8 controls with normal hearing, and 8 children with Connexin 26	Mean age 6.7 months; range 4.8–8.9 months	Fine motor Gross motor
Nishida et al, 2020[36]	Japan	Prospective cohort	42 infants with cCMV (24 with “clinical symptoms” and an additional 7 with isolated abnormal neuroimaging), cohort overlaps with Yamada et al, [22] and Tanimura et al [63]	Testing performed ~ 18 months corrected age	Global
Noyola et al, 2001[42] **	USA	Retrospective cohort	41 children with symptomatic cCMV	Median age at last follow-up was 5.7 years, range 11 months-13 years	Cognitive
Numazaki et al, 2004[31] **	Japan	Prospective cohort	37 infants with cCMV (5 symptomatic)	≥7 years old	Cognitive
Oosterom et al, 2015[34] **	Netherlands	Prospective cohort	36 infants with cCMV (26 symptomatic) with neuroimaging	Asymptomatic children: Age range 1.5 to 5.4 years; Symptomatic children: Age range 1.1 to 3.0 years	Global
Pathirana et al, 2020[25]	South Africa	Prospective matched case-control cohort	46 infants with cCMV (3 symptomatic, 43 asymptomatic) and 84 matched uninfected controls. 34 cases and 74 controls completed assessments.	6 and 12 months	Global Fine motor Gross motor Speech/ language Cognitive
Pearl et al, 1986[38]	United Kingdom	Cross-sectional case-control	41 children with cCMV (5 symptomatic) and 74 controls	Testing performed ~ 2 years old	Global Fine motor Gross motor Speech/ language
Puhakka et al, 2019[20]	Finland	Prospective matched case-control cohort	40 children with cCMV (4 symptomatic) and 54 matched controls	Testing performed ~ 18 months	Global Fine motor Gross motor Speech/ language
Reynolds et al, 1974[64]	USA	Prospective case-control cohort	18 infants with “inapparent” cCMV and 18 controls	Mean 38 months, range 21–77 months	Cognitive
Saigal et al, 1982[65]	Canada	Prospective matched case-control cohort	46 children with cCMV and 40 matched controls	Testing performed at 3 years and 5 years	Cognitive
Shan et al, 2009[39]	China	Prospective case-control	41 infants with asymptomatic cCMV, and 21 controls	Testing performed at 6 months and 12 months of age	Cognitive Gross motor
Suzuki et al, 2008[66] *	Japan	Retrospective cohort	19 children with cCMV (16 symptomatic)	Mean 8 years, range 3–12 years	Global

Study	Country	Study design	N and participants*	Age at neurodevelopmental assessment	Developmental domain(s) assessed
Tanimura et al, 2021[63]	Japan	Prospective cohort	15 infants with symptomatic cCMV who received fetal ± neonatal treatment, and 19 who received neonatal treatment only. Cohort overlaps with Yamada et al, [22] and Nishida et al[36]	Testing performed ~ 18 months corrected age	Global
Townsend et al, 2013[26]	Sweden & the United Kingdo m	Retrospective case-control cohort	UK cohort: n=176 infants with cCMV (19 symptomatic) and 214 controls. Swedish cohort (n=76 cCMV and 62 controls), overlaps with cohort reported by Ivarsson et al. [28]	Last study visit occurred at 5–7 years old	Global Cognitive
Yamada et al, 2020[22]	Japan	Prospective cohort	19 infants with symptomatic cCMV (cohort overlaps with Nishida et al, and Tanimura et al) [36,63]	Testing performed ~ 18 months corrected age	Global
Zhang et al, 2007[29]**	China	Prospective matched case-control cohort	49 children with asymptomatic cCMV and 55 matched controls	Study visits occurred at ~2 years, range 18–36 months, and again at ~5 years, range 48–72 months	Global Gross motor Speech/language Cognitive

*Definitions of symptomatic and asymptomatic congenital cytomegalovirus as defined in each study, which were highly variable

**Denotes that outdated terminology to describe intellectual/cognitive developmental delay or disability (e.g., mental retardation) was used in the original publication, which the authors have updated to “intellectual disability” or “intellectual deficit”

Table 4.

Criteria used by studies included in the scoping review to categorize neonates as having symptomatic congenital cytomegalovirus

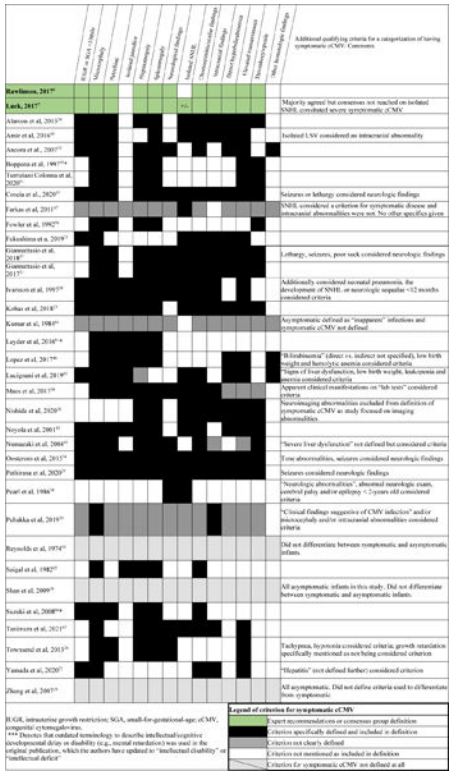

Table 5a.

Overview of studies of measuring global developmental outcomes in infants and children with congenital cytomegalovirus infection included in the scoping review

Global development			
Study	**Instruments**	**Measures and outcomes of global development**	**Results***
Alarcon et al, 2013[24]	BSID-III[48] WISC-III[67] WISC-IV[68] MABC-2[69]	Neurodevelopmental disability classified as: A) Absent of Mild (no or mild CP, BSID-III cognitive, language, motor score >84, or global IQ >70; normal hearing; normal vision, and no behavioral abnormalities), B) Moderate (GMFCS score II-III; BSID-III cognitive, language, motor score 70–84, or global IQ 50–70; seizures controlled with anticonvulsants; hearing deficit compensated by aids; visual deficit with useful vision or behavior or emotional problems, including affective problems, anxiety, somatic complaints, attention deficit/hyperactivity, oppositional defiant or rule-breaking behavior), or C) severe (GMFCS score IV-V; BSID-III cognitive, language, motor score <70, or global IQ <50; seizures not controlled with anticonvulsants; hearing loss not corrected by hearing aids; no useful vision or pervasive developmental disorder)	In this cohort of 23 children with symptomatic cCMV, 7 (30%) and 8 (34%) of infants had moderate or severe neurodevelopmental disabilities respectively. 15 (65%) had at least 1 neurodevelopmental disability, and 11 (47%) had two or more.
Ancora et al., 2007[33]	Brunet-Lezine test[70]	Psychomotor development = developmental/chronologic age to calculate DQ. DQ ≤0.85 considered abnormal	In this cohort of neonates with asymptomatic and symptomatic cCMV, 8/57 infants who also had severe intracranial involvement met criteria for “poor psychomotor development” with median DQ of 76.8, range 67–79. 42/45 infants without cerebral US abnormalities had “normal” psychomotor outcomes.
Coscia et al., 2020[57]	GMDS-III[71]	General Quotient <85 considered neurodevelopmental delay	In this cohort of 91 children with cCMV (37 symptomatic), 28 (30.8%) children met criteria for global neurodevelopmental delay. There was no difference in risk of neurodevelopmental delay by trimester of infection, or primary vs. non-primary infection.
Fukushima et al., 2019[21]	KSPD[72]	Global development categorized as: A) No Impairment (DQ>80 and no hearing dysfunction); B) Mild Sequelae (unilateral hearing dysfunction or a DQ of 70–79) or C) Severe Sequelae (DQ < 70, bilateral hearing dysfunction requiring hearing aids, blindness or epilepsy requiring anti-epileptic drugs)	9 (42.7%) children had DQ <70, and 12 (57.1%) had DQ ≥ 70, 6 (28.6%) were in the No Impairment group, 4 (19%) in the Mild Sequelae group and 11 (52.4%) in the Severe Sequelae group.
Giannattasio et al, 2017[31]	GMDS-ER [73]	“Impaired neurologic outcome” defined as DQ or IQ <70, motor delay requiring rehabilitation, epilepsy or behavioral or emotional problems	32 (36.3%) symptomatic, 6 (8.5%) of asymptomatic children met criteria for a “impaired neurologic outcome”.
Giannattasio et al, 2018[37]**	GMDS-ER[73]	“Impaired neurologic outcome” defined as DQ or IQ <70, motor delay requiring rehabilitation, epilepsy or behavioral or emotional problems.	An “impaired neurologic outcome” was observed in 55 (32.3%) cases, including 9 with mild-to-moderate developmental/intellectual delay (not defined), 4 with gross motor delay, 1 with epilepsy and 12 with behavioral or emotional problems.
Ivarsson et al, 1997[28]	WISC[53]	Mean WISC score	No difference in global development at 89 weeks between cases and controls.
Kobas et al, 2018[23]	BSID-II[74] BSID-III[48] MDS[32] K-ABC Kaufman,	Abnormal neurodevelopmental outcomes are defined as having any one test component or subscale score >1 SD below the mean.	6 (23%) children had an “abnormal neurodevelopmental score” at ≥ 6 months of age (including 1 had who had isolated language delay in the setting of moderate unilateral hearing loss)

Global development			
Study	**Instruments**	**Measures and outcomes of global development**	**Results***
	1983 #952} WPPSI-R[75]		
Kumar et al, 1984[44]	WISC-R[76] WPPSI[77] Bender-Gestalt test[78]	IQ scores and standardized test scores in relation to chronological age for speech/language measures	Mean cognitive and speech/language scores did not differ between groups.
Leyder et al, 2016[61]**	BSID-II[74] WISC-III[76]	Categorized based on global "neurologic outcomes" as A) Normal (scores within normal limits); B) Mild Impairment (abnormal neurological findings slightly affecting normal function); or C) Severe Impairment (major psychomotor impairment (definition not included), intellectual disability (IQ<70), or cerebral palsy)	21 (60.0%) children were in the Normal neurologic outcomes group, 6 (17.1%) were in the Mild Impairment group (4 with psychomotor delay but not CP, 2 with behavioral problems), and 2 (5.7%) were in the "Severe Impairment" group (both with CP and epilepsy, and 1 with IQ <70).
Lucignani e al, 2019[62]	BSID-III[48]	"Neurological impairment" defined as having severe neuromotor delay or CP, a score of <85 on the BSID-III at 6, 12, 18, or 24 months of life, and/or score <70 on the MDI or PDI. Hearing loss, vision loss or "neurological impairment was considered as "adverse neurological outcomes" [58]	30 (68.1%) of children developed "adverse neurological outcomes", including 20 (74.0%) of symptomatic and (58.8%) of asymptomatic infants.
Nishida et al, 2020[36]	KSPD[72]	"Neurodevelopmental impairment" classified as a DQ < 80, hearing dysfunction, blindness, or epilepsy requiring anti-epileptic drugs	Of the 38 infants with developmental follow-up, 19 (50.0%) had "normal" and 19 (50.0%) had "neurodevelopmental impairment". The latter group had a higher number of infants with clinical symptoms at birth, brain MRI findings and treatment with antiviral therapy.
Oosterom et al, 2015[34]**	GMDS[32] BSID-III[48]	Abnormal DQ defined as –1 SD (DQ ≤ 85) in both tests	"Neurodevelopmental impairment" was found in 2/5, 1/3, 0/4 and 7/17 surviving children infected in the first, second, third and unknown trimesters of pregnancy. 8 (50.0%) of infants with severe abnormalities on CUS had "poor neurodevelopmental outcomes", as did 10 (77%) of those with severe abnormalities seen on MRI.
Pathirana et al, 2020 [25]	BSID-III[48]	Scores ≥ 2 SD below the mean composite or subscale score (100, SD 15) were defined as delayed.	No difference in neurodevelopmental delay at 12 months between cases (largely asymptomatic) and controls (6% vs. 4%, p=.96). Only one infant with cCMV had global delay.
Pearl et al, 1986[27]	GDS[79]	DQ was calculated as the mean of five subscales (locomotor function, personal social skills, language development skills, eye-hand coordination, and fine motor performance skills)	DQs of children with symptomatic cCMV were on average 35.6 points lower than that of controls (p<.0001), whereas children with asymptomatic cCMV had DQ's that were no different than controls.
Puhakka et al, 2019[20]	GMDS[32]	General quotient	There were no statistically significant differences in the mean general quotient scores between children with cCMV (36/40 asymptomatic) vs controls (Mean = 101.0 vs. 101.6, p = .56)
Suzuki et al, 2008[39] 66**	KSPD[72]	Developmental disability defined as a DQ <70	No significant differences in the incidence of developmental disability between the epileptic group 6/7 vs. non-epileptic group 7/12 (p= 0.3).
Tanimura et al, 2021[63]	KSPD[72]	Overall development categorized as: A) Normal Development: No sequelae and DQ ≥ 80; B) Mild Impairment: Unilateral SNHL or mild developmental delay with a DQ of 70–79; or C) Severe Impairment: Bilateral SNHL requiring hearing aids, epilepsy requiring antiepileptic drugs, or severe developmental delay (an overall DQ < 70).	Of the surviving children with follow-up data at 18 months, a lower proportion of children who received fetal treatment had "severe impairment" at 18 months, versus those who received neonatal treatment alone (18.2 % vs 64.3 %, p < 0.05).
Townsend et al, 2013[26]	GDS[79]	Global development categorized as A) Normal development : "No problems identified"; B) Mild impairment: unilateral SNHL, or mild	UK cohort: Mean development score at 2 years to was similar among children with cCMV and no neurological symptoms and controls, previously reported

Global development			
Study	**Instruments**	**Measures and outcomes of global development**	**Results***
		bilateral SNHL, or mild gross motor delay, or clinically recognized language or developmental delay; C) Moderate impairment = moderate to severe “bilateral SNHL without any other identified problem, mild bilateral SNHL and mild cerebral palsy, or moderate learning difficulties”; D) Severe impairment = severe disability or multiple problems, for example, moderate/severe bilateral SNHL with CP, severe learning difficulties.	by Ivarsson et al. [28] No “developmental or intellectual differences” between cases or controls at 21 months or 7 years respectively.
Yamada et al, 2020[22]	KSPD[72]	DQ; Outcomes classified as: A) No Impairment (DQ ≥80 and normal hearing); B) Mild Sequelae (unilateral SNHL and/or DQ of 70–79); or C) Severe Sequelae (DQ < 70, bilateral SNHL requiring hearing aids, blindness, and/or epilepsy requiring anti-epileptic drugs).	8 (42.1%) children had a DQ ≥ 80, 2 (10.5%) had a DQ 70–79, and 6 (31.6%) had a had a DQ <70. 7 (36.8%) children were in the No Impairment group, 4 (21.1%) in the Mild Sequelae group, and 8 (42.1%) in the Severe Sequelae group.
Zhang et al, 2007[29]**	GDS[79] WPPSI [76]	DQ at 2 years = composite score of GDS subscales FSIQ at 5 years = composite of Verbal IQ and Performance IQ;	Children with asymptomatic cCMV had lower global DQ as compared to matched controls at 2 and 5 years respectively, driven by lower DQ language development (t = 3.25, p = 0.002) and Verbal IQ scores (t = 3.88, p =0.000).

Table 5b.

Overview of studies of measuring fine developmental outcomes in infants and children with congenital cytomegalovirus infection included in the scoping review

Fine motor			
Study	**Instruments**	**Measures and outcomes of fine motor development**	**Results***
Farkas et al, 2011[47]	BSID-III[48] WRAVAMA – Pegboard subtest[80]	Pegboard or BSID-III fine motor subscale standard score	No differences were in fine motor performance between cases and controls.
Ivarsson et al, 1997[28]	Circle test	Abnormal (vs. normal) results on the Circle test	No difference in fine motor scores at 86 months between cases and controls.
Maes et al, 2017[38]	PDMS-2[81]	Fine Motor Quotient	No differences were in fine motor performance between any of the groups.
Pathirana et al, 2020[25]	BSID-III[48]	Score ≥ 2 SD below the mean fine motor subscale score (100, SD 15) = neurodevelopmental delay	Two cases and one control (n=2/35 and 1/74) had motor delay (composite of gross motor and fine motor subscale scores) at 12 months. This difference was not statistically significant.
Pearl et al, 1986[27]	GDS[79]	Eye/hand coordination subscale mean score	There were no differences in eye/hand coordination between children with asymptomatic cCMV and controls. Children with symptomatic cCMV had scores ~ 25 standard points lower than controls or those with asymptomatic cCMV. 2/5 children with symptomatic cCMV had spastic quadriplegia.
Puhakka et al, 2019[20]	GMDS[32]	Sub quotient of Eye-hand coordination subscale	No differences were in fine motor performance between children with cCMV (36/40 asymptomatic) and controls (Mean = 103.2 vs. 101.7, p =0.65).

Table 5c.

Overview of studies of measuring gross motor outcomes in infants and children with congenital cytomegalovirus infection included in the scoping review

Gross motor developmental outcomes			
Study	**Instruments**	**Measures and outcomes of gross motor development**	**Results***
Alarcon et al, 2013[24]	MABC-2[69]	GMFCS categories for those with cerebral palsy. Subset of children aged >3 years without CP (n=11/23), normal, abnormal or borderline scores on the MABC-2	10/23 surviving children (all with symptomatic cCMV) had cerebral palsy, 5 of which had GMFCS scores ≥ IV (indicating a need for assisted or powered wheeled mobility). No children without cerebral palsy had abnormal or borderline total scores on the MABC-2.
Ivarsson et al, 1997[28]	Stott test[82]	Abnormal (vs. normal) results on the Stott test	There was no difference in gross motor scores between children with cCMV and controls at 86 months.
Maes et al, 2017[38]	PDMS-2[81]	Gross Motor Quotient	Symptomatic cCMV with SNHL group had lowest gross motor performance, significantly lower than the asymptomatic group, control group and connexin 26 group (all p's <.01).
Pathirana et al, 2020[25]	BSID-III[48]	Scores ≥ 2 below the mean for the motor composite scale (summary scale of gross and fine motor subscales) was defined as neurodevelopmental delay.	No difference in motor scores between infants with cCMV and controls
Pearl et al, 1986[27]	GDS[79]	Locomotion subscale	No difference in gross motor outcomes between children with asymptomatic cCMV and controls. The subset of children with symptomatic cCMV (2/5 had spastic quadriplegic CP) had significantly lower gross motor scores as compared to asymptomatic children and controls.
Puhakka et al, 2019[20]	GMDS[32]	Sub quotient of the Locomotor subscale	There were no statistically significant differences in the mean locomotor subscale mean between children with cCMV (36/40 asymptomatic) and controls (Mean = 100.8 vs. 100.5, p=.72)
Shan et al, 2009[39]	BSID[48]	BSID MDI and BSID PDI standard scores	No difference in MDI scores between the control group and cCMV group (all asymptomatic) at 1 year of age
Zhang et al,2007[29]**	GDS[79]	Locomotion subscale score	At 2 years there was no difference in motor skills, between the two groups (children with asymptomatic cCMV and matched controls)

Table 5d.

Overview of studies of measuring speech and language outcomes in infants and children with congenital cytomegalovirus infection included in the scoping review

Speech/language			
Study	**Instruments**	**Measures and outcomes of speech and language development**	**Results***
Turriziani Colonna et al, 2020[51]	BVL 4–12[83] TFL Griffiths Battery[32]	"Language disorders" defined as scores on language tests outside the normal range for each instrument according to child age	"Language disorders" (whether expressive, receptive, or associated with SNHL not stated) identified in 3 symptomatic children with CNS involvement and 3 asymptomatic children.
Farkas et al, 2011[47]	BSID-III[48] PPVT-IV[49]	Receptive Language (PPVT or BSID-III receptive language score)	Children with cCMV (mostly asymptomatic) did not differ from the control group in terms of receptive language scores.
Kumar et al, 1984[44]	WISC-R[84]WPPSI[77] Ammons Quick test[85] Northwestern Syntax Screening Test[50]	Standardized test scores in relation to chronological age for speech/language measures	Mean speech/language scores did not differ between children with cCMV (severity not stated) and controls
Lopez et al, 2017[46]	WISC-III[76]WASI[86] PPVT-R[87] Expressive One Word Picture Test Revised[88]	Standardized receptive and expressive vocabulary scores (Mean 100, SD 15).	Expressive vocabulary scores were not different between the 3 groups (asymptomatic cCMV without SNHL, with SNHL and sibling controls). Receptive vocabulary scores were lower among those with asymptomatic cCMV and SNHL vs. those with asymptomatic cCMV with normal hearing, and controls
Pathirana et al, 2020[25]	BSID-III[48]	Scores ≥ 2 SD below the mean score (Mean 100, SD 15) on the language composite scale was defined as delayed	No difference in language delays (presence vs. absence) at 12 months in cCMV cases (mostly asymptomatic) and controls
Pearl et al, 1986[38]	GDS[79]	Sub quotient of the Hearing and Language subscale.	There was no difference in Hearing and Language outcomes between children with asymptomatic cCMV (defined as having no 'neurologic deficit' or SNHL) and controls. Subset of children with symptomatic cCMV (2/5 had spastic quadriplegic CP, and 4/5 had SNHL) had significantly lower scores as compared to asymptomatic children and controls.
Puhakka et al, 2019[20]	GMDS[32]	Sub quotient of the Hearing and Language subscale.	There were no statistically significant differences in the hearing and language subscale scores between children with cCMV (36/40 asymptomatic) and controls. (Mean = 101.2 vs. 102.0, p=.47)
Zhang et al, 2007[29]**	GDS[79] WPPSI[76]	DQ Language subscale score Verbal IQ score	As compared to uninfected controls, children with asymptomatic cCMV had lower DQ language development at 2 and 5 years respectively (t = 3.25, p = 0.002) and Verbal IQ scores (t = 3.88, p = 0.000)

Table 5e.

Overview of studies of measuring cognitive/intellectual outcomes in infants and children with congenital cytomegalovirus infection included in the scoping review

Cognitive/Intellectual			
Study	**Instruments**	**Measures and outcomes of speech and language development**	**Results***
Alarcon et al, 2013[24]	BSID-III[48] WPPSI-III[89] WISC-IV[68]	"Cognitive deficit" or "severe cognitive deficit" = BSID-III cognitive or language score of < 85 or <70, respectively, or global IQ ≤ 70 or 50 respectively	12 (52.2%) children (all symptomatic) met criteria for a "cognitive deficit" including 8 meeting criteria for a "severe cognitive deficit"
Amir et al, 2016[40]	BSID-III[48]	BSID-III developmental index	In the subgroup of 27 children, the BSID-III mean developmental index was 102.6±10.3 (range 85–127) in the normal range. None of the children showed "any cognitive delay"
Boppana et al, 1997[55] **	BSID[90]SBIS[73] ABDP[91] WPPSI[76]WISC-R[84]	Intellectual disability = IQ <70 (what instruments among the six listed that were used to determine this score were not explicitly stated)	17 (47.2%) children met criteria for intellectual disability (IQ <70), with severe intellectual disability in 13 (36.1%) (IQ <50). All but one child meeting criteria for an intellectual disability had intracranial findings on a CT scan.
Turriziani Colonna et al, 2020[51]	WPPSI-III[76]WPPSI[76]WISC -IV [44] Leiter-R non-verbal scale[92]	IQ score lower than normal <70, borderline 70 ≤ IQ ≤ 84, normal 85 ≤ IQ ≤ 115, higher than the norm ≥ 116	30 (90%) had normal range IQ scores or greater, with 45% scoring above the normal range. 3 asymptomatic children had borderline IQ scores. IQ score lower than the normal range identified in 2 asymptomatic children and 1 symptomatic child
Farkas et al, 2011[47]	BSID-III[48], K-ABC Kaufman, 1983 #952}	Cognitive score (total K-ABC or BSID-III cognitive score)	Children with cCMV did not differ from the control group in terms of cognitive, scores
Fowler et al, 1992[56]	BSID[90] SBIS[73] ABDP[91]WPPSI[76] WISC-R[84]	IQ ≤ 70 (vs not)	9 (9%) of children had IQ ≤ 70, all of whom were in the primary- infection group vs. non-primary group (13% vs. 0%, p=.03).
Ivarsson et al, 1997[28]	GDS{Gesell, 1925 #958, WISC[50]	Mean WISC score	No difference in g cognitive scores at 86 months between cases and controls.
Kumar et al, 1984[44]	WISC-R[76] WPPSI[76]Bender-Gestalt test[78] Ammons Quick test[85]	IQ scores and standardized test scores in relation to chronological age for speech/language measures	Mean cognitive scores did not differ between groups (17 asymptomatic and 21 controls).
Lopez et al, 2017[46]	WISC-III[76] WASI[86]	Scores on all tests have a mean of 100 (SD 15–16). Children categorized as "at risk of intellectual impairment" if IQ scores <85.	Verbal intelligence and non-verbal scores were not different between the 3 groups. FSIQ did not differ between children with normal hearing and controls. Children with SNHL had FSIQ 7 points lower than hearing controls, which is a composite of subscales including verbal and non-verbal intelligence. Lower FSIQ among those with SNHL likely due to SNHL (verbal intelligence score) and not cCMV.
Noyola et al, 2001[42]	BSID[90] K-ABC[93] WISC-R[84]	Cognitive scores categorized as: Normal Intelligence (IQ/DQ ≥90), Intellectual Disability (IQ/DQ <70), and Severe Intellectual Disability (IQ/DQ <50)	Of the 41 children, 12 (29.2%) were in the Normal Intelligence, 10 (24.3%) had IQ/DQ of 70–89 (category name not provided), and 4 (9.7%) were in the Severe Intellectual Disability group. Microcephaly at birth had the highest specificity, and abnormal head CT had the highest sensitivity for predicting intellectual disability.
Numazaki et al, 2004[41] **	WISC-III[76]	Cognitive scores categorized as: Normal Intelligence (IQ/DQ ≥90), Intellectual Disability (IQ/DQ <70), and Severe Intellectual Disability (IQ/DQ <50)	Of the 21 infants with asymptomatic cCMV with follow-up for at least 7 years, 18 (85.7%) had normal intelligence and 3 (14.3%) met criteria for Intellectual Disability, later determined to be borderline. No children with asymptomatic cCMV met criteria for a Severe Intellectual Disability.

Pathirana et al, 2020[25]	BSID-III[48]	Scores ≥ 2 SD below the mean composite score (100, SD 15) were defined as neurodevelopmental delay	No difference in neurodevelopmental delay at 12 months between cases (largely asymptomatic) and controls (6% vs. 4%, p=.96). Neurodevelopmental delay was identified at 12 months in 1 asymptomatic infant (motor), 1 symptomatic infant with CNS involvement (global delays) and 3 controls (2 language and 1 motor delay).
Saigal et al, 1982[65]	SBIS [94]	Stanford-Binet scores	There were no differences in IQ scores measured at 3 and 5 years old between cases and controls (97.0 ± 16.5 vs. 100.6 ± 15.6, and 107.8 ± 16.6 vs 106.5 ± 9.5).
Shan et al, 2009[39]	BSID[90]	BSID MDI and BSID PDI scores	No difference in MDI and PDI scores between the control group (107.49 ± 11.31 and 107.19 ± 10.98) and cCMV group at 1 year of age (107.21 ± 9.96 and 108.31 ± 11.25).
Townsend et al, 2013[26]	GDS[79] WPPSI[76]	Development score (Measure of cognitive development) and IQ	UK cohort: no differences in IQ scores (Overall, Performance or Verbal) measured at age 5 years. Swedish cohort: Previously reported by Ivarsson et al.[28]
Zhang et al, 2007[29] **	GDS[79] WPPSI[76]	DQ at 2 years = composite score of GDS subscales; FSIQ at 5 years = composite of Verbal IQ and Performance IQ Categorical intelligence outcome: A) Normal intelligence IQ/DQ ≥90); B) (no name given) IQ/DQ 89–71; C) Intellectual disability IQ/DQ < 70); and D) Severe intellectual disability (IQ/DQ < 50).	Children with asymptomatic cCMV had lower DQ and FSIQ scores as compared to controls at 2 and 5 years respectively, driven by lower DQ language development (t = 3.25, p = 0.002) and Verbal IQ scores (t = 3.88, p = 0.000). The prevalence of intellectual disability was similar between both groups.

ABDP, Alpern-Boll Developmental Profile; BSID, Battery for the Assessment of Language; BVL 4–12; Bayley Scale of Infant Development; BSID-II, Bayley Scales of Infant and Toddler Development Second Edition; BSID-III, Bayley Scales of Infant and Toddler Development Third Edition; CP, cerebral palsy; CT scan, computerized tomography scan; FSIQ, Full Scale IQ; GDS, Griffiths Developmental Scale; GMDS, Griffiths Mental Development Scale; GMDS-II, Griffiths Mental Development Scale II; GMDS-III, Griffiths Mental Development Scale III; GMDS-ER, Griffiths Mental Developmental Scales Version extended revised; GMFCS, Gross Motor Function Classification System; K-ABC, Kaufman Assessment Battery for Children; KSPD. Kyoto Scale of Psychological Development; MABC-2, Movement Assessment Battery for Children – Second Edition; MDI, Mental development index; PDI, Psychomotor development index; PDMS-2, Peabody Developmental Motor Scales, Second Edition; PPVT, the Peabody Picture Vocabulary Test; PPVT-IV, the Peabody Picture Vocabulary Test, Fourth Edition; PPVT- R, the Peabody Picture Vocabulary Test-Revised; SBIS, Stanford-Binet Intelligence Scale; SNHL, Sensorineural Hearing Loss; WASI, Wechsler Abbreviated Scale Intelligence; WISC, Wechsler Intelligence Scale for Children; WISC-III, Wechsler Intelligence Scale for Children- III; WISC-IV, Wechsler Intelligence Scale for Children, Fourth Edition; WISC-R, Wechsler Intelligence Scale for Children-Revised; WPPSI, Wechsler Preschool and Primary Scale of Intelligence; WPPSI-III, Wechsler Preschool and Primary Scale of Intelligence, Third Edition; WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence-Revised; WRAVMA – Pegboard subset, Wide Range Assessment of Visual Motor Abilities - Pegboard subtest

*Definitions of symptomatic and asymptomatic congenital cytomegalovirus as defined in each study, which were highly variable

**Denotes that outdated terminology to describe intellectual/cognitive developmental delay or disability (e.g., mental retardation) was used in the original publication, which the authors have updated to “intellectual disability” or “intellectual deficit”