Neurodevelopmental outcomes in children with congenital CMV:
Results of a systematic review

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Disclosures

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Learning Objectives

1. To recognize the importance of understanding and predicting neurodevelopmental outcomes in children with cCMV
2. To summarize the literature to date on neurodevelopmental outcomes in children with cCMV
3. To examine limitations in the present literature and biases

Background

- Congenital CMV is common
- Wide spectrum of outcomes
- Hard to predict with certainty

Symptomatic vs. Asymptomatic

Study 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

Definitions

- **Symptomatic cCMV disease** - clinically apparent sequelae by physical exam, fundoscopic exam, imaging and/or laboratory studies.

- **Asymptomatic cCMV infection** - No clinically apparent sequelae by physical exam, fundoscopic exam, imaging and/or laboratory studies. Infants with isolated SNHL and no other findings are included.

Definitions

- **Neurodevelopmental outcome** - Level of skill development in infants or children as compared to typical development for age

- **Neurodevelopmental delay** - Level of skill development which is greater than two standard deviations lower than typical development for age.

- **Neurodevelopmental domain -** Developmental areas underlying functional or observable performance and abilities of a child.

Neurodevelopmental domains

- Global development
- Fine motor
- Gross motor
- Speech/language
- Intellectual/cognitive

Systematic scoping review

- **PRIMSA guidelines were followed**
- **PubMed, PsychInfo and Embase**

Search terms

- Neurodevelopmental outcomes
- Developmental delay
- Gross motor
- Fine motor
- Congenital cytomegalovirus
- Cytomegalovirus infections

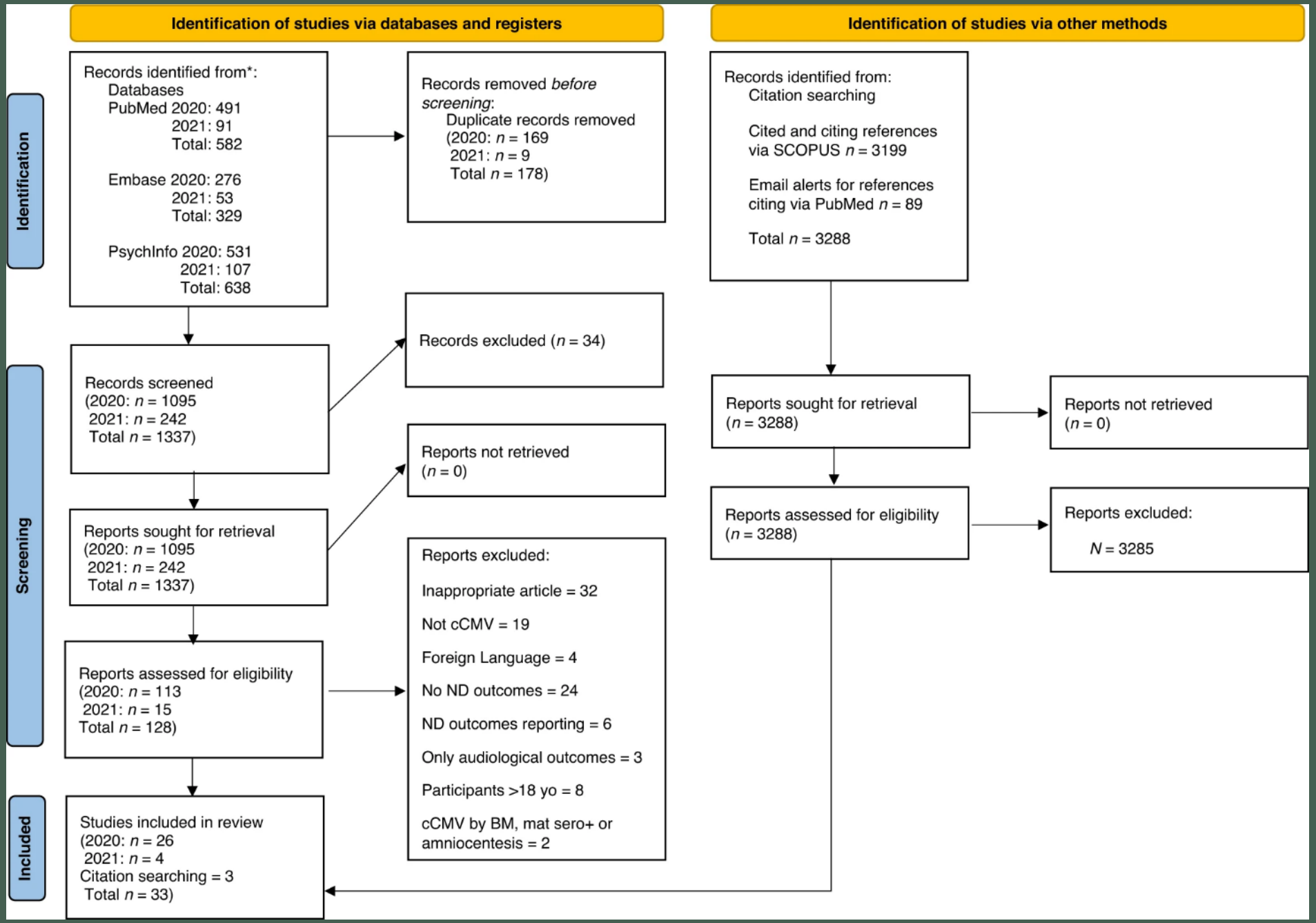
Inclusion

- Peer reviewed
- Children <18 yo
- Confirmed cCMV
- Measured neurodevelopmental outcomes

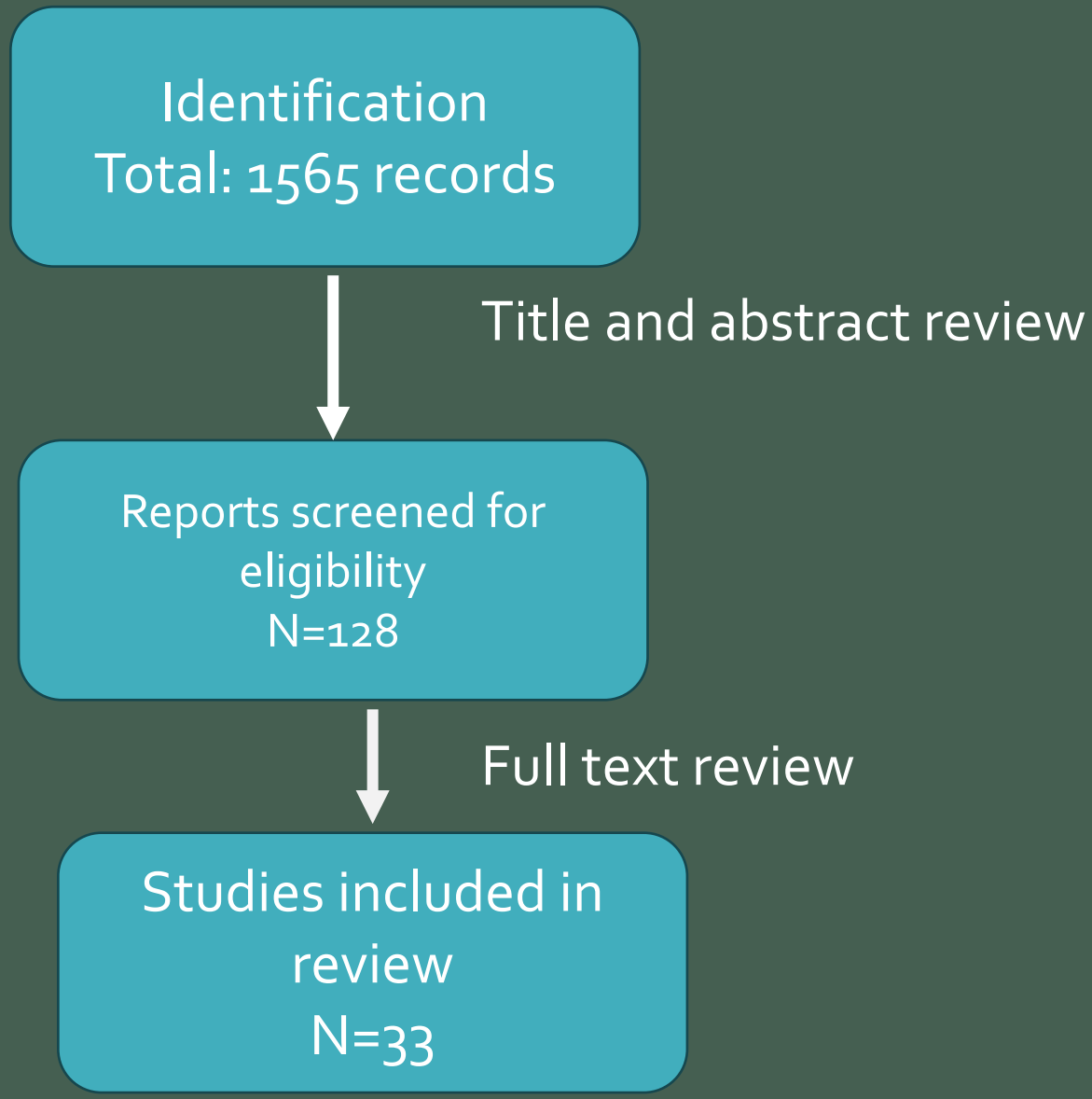
Exclusion

- Non-English language
- Reviews, conference abstracts
- Focus on audiologic outcomes

PRISMA


Identification of studies via databases and registers
Identification of studies via other methods
Identification
Screening
Included
Records identified from*:
Databases
PubMed 2020: 491
2021: 91
Total: 582
Embase 2020: 276
2021: 53
Total: 329
PsychInfo 2020: 531
2021: 107
Total: 638
Records removed *before screening*:
Duplicate records removed
(2020: *n* = 169
2021: *n* = 9
Total *n* = 178)
Records identified from:
Citation searching
Cited and citing references via SCOPUS *n* = 3199
Email alerts for references citing via PubMed *n* = 89
Total *n* = 3288
Records screened
(2020: *n* = 1095
2021: *n* = 242
Total *n* = 1337)
Records excluded (*n* = 34)
Reports sought for retrieval
(*n* = 3288)
Reports not retrieved
(*n* = 0)
Reports sought for retrieval
(2020: *n* = 1095
2021: *n* = 242
Total *n* = 1337)
Reports not retrieved
(*n* = 0)
Reports assessed for eligibility
(*n* = 3288)
Reports excluded:
N = 3285
Reports assessed for eligibility
(2020: *n* = 113
2021: *n* = 15
Total *n* = 128)
Reports excluded:
Inappropriate article = 32
Not cCMV = 19
Foreign Language = 4
No ND outcomes = 24
ND outcomes reporting = 6
Only audiological outcomes = 3
Participants >18 yo = 8
cCMV by BM, mat sero+ or amniocentesis = 2
Studies included in review
(2020: *n* = 26
2021: *n* = 4
Citation searching = 3
Total *n* = 33)

PRISMA

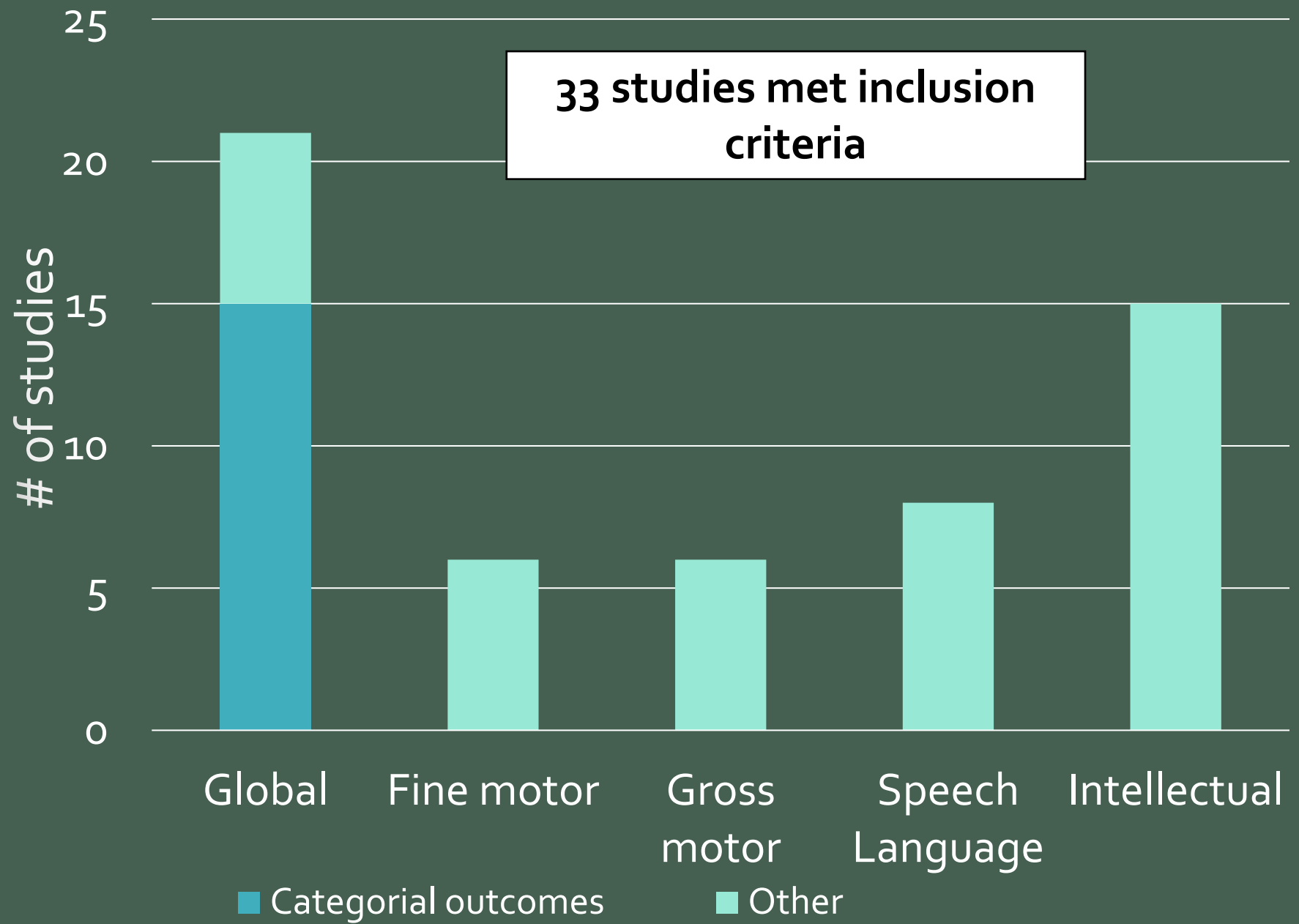

Identification
Total: 1565 records
Title and abstract review
Reports screened for eligibility
N=128
Full text review
Studies included in review
N=33

Disease severity

Examined each study's definition of symptomatic vs. asymptomatic vs. other categorization

Results

33 studies met inclusion criteria



31/33 Differentiated symptomatic vs. not

Disease severity

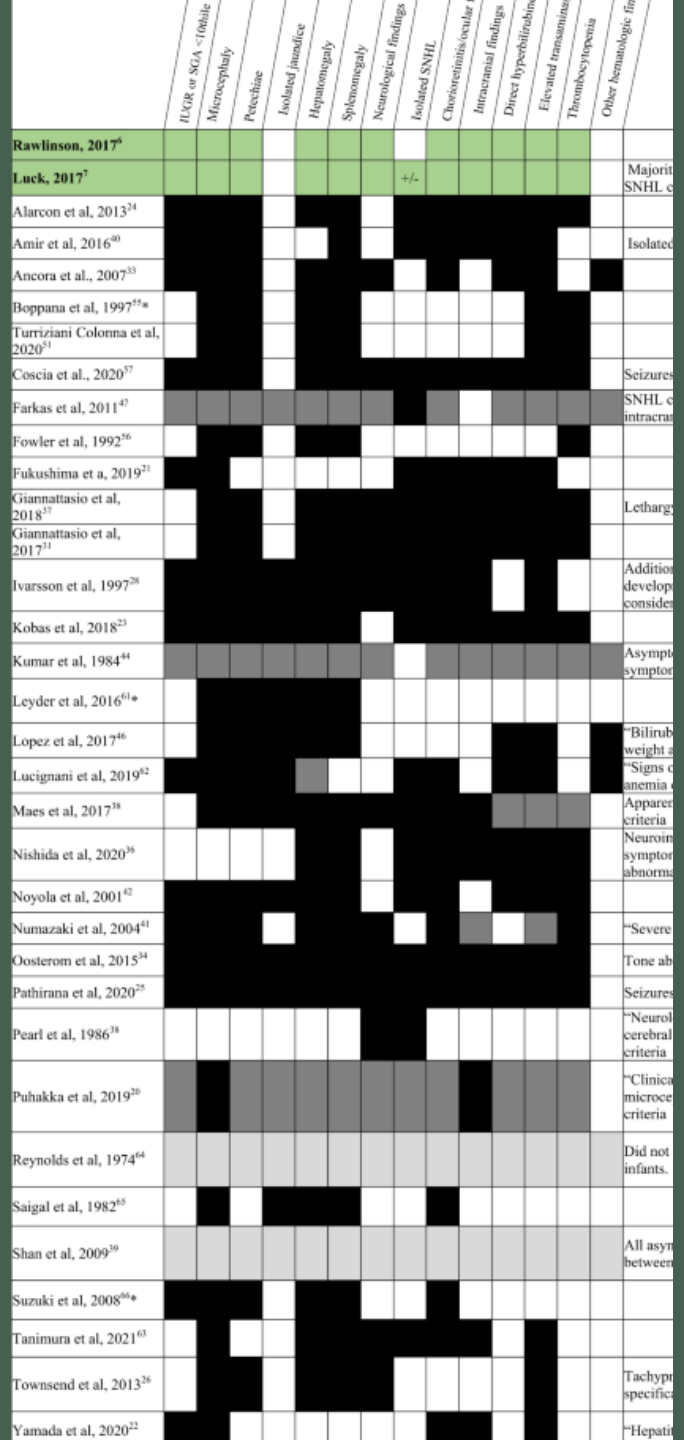
- Variation in definitions of disease severity

Symptomatic

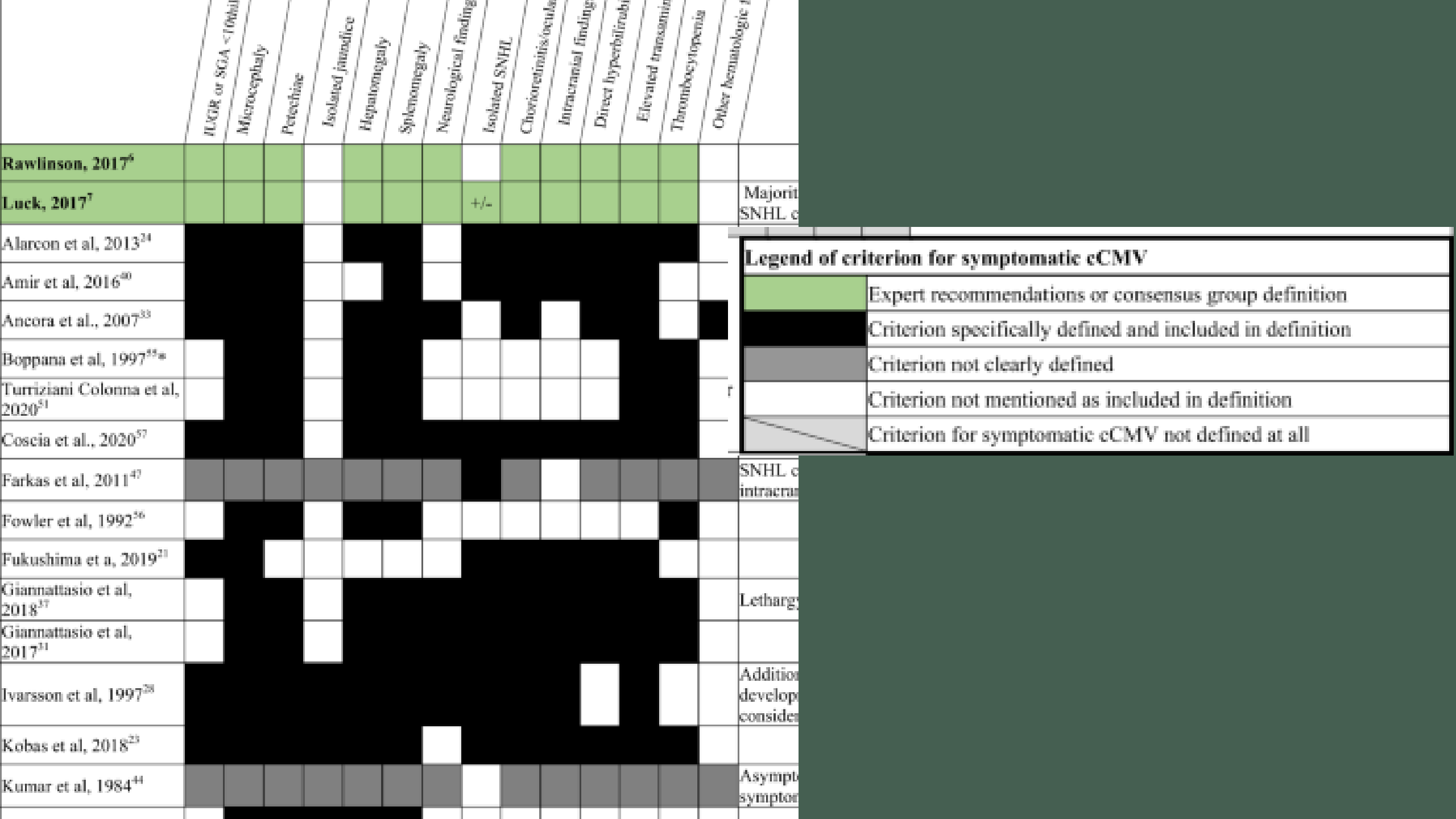
- Isolated SNHL
- Preterm birth
- Small for gestational age
- Isolated LSV

Not symptomatic

- Isolated SNHL
- Preterm birth
- Small for gestational age
- Isolated LSV



Legend of criterion for symptomatic cCMV	
	Expert recommendations or consensus group definition
	Criterion specifically defined and included in definition
	Criterion not clearly defined
	Criterion not mentioned as included in definition
	Criterion for symptomatic cCMV not defined at all


IUGR or SGA <10th
Microcephaly
Petechiae
Isolated jaundice
Hepatomegaly
Splenomegaly
Neurological findings
Isolated SNHL
Chorioretinitis/ocular
Intracranial findings
Direct hyperbilirubi
Elevated transamin
Thrombocytopenia
Other hematologic
Rawlinson, 2017[6]
Luck, 2017[7]
+/-
Majorit
SNHL c
Alarcon et al, 2013[24]
Amir et al, 2016[40]
Ancora et al., 2007[53]
Boppana et al, 1997[55]*
Turriziani Colonna et al, 2020[51]
Coscia et al., 2020[57]
Farkas et al, 2011[47]
SNHL c
intracra
Fowler et al, 1992[56]
Fukushima et a, 2019[21]
Giannattasio et al, 2018[37]
Letharg
Giannattasio et al, 2017[41]
Ivarsson et al, 1997[28]
Additio
develop
consider
Kobas et al, 2018[23]
Kumar et al, 1984[44]
Asympt
sympto
Legend of criterion for symptomatic cCMV
Expert recommendations or consensus group definition
Criterion specifically defined and included in definition
Criterion not clearly defined
Criterion not mentioned as included in definition
Criterion for symptomatic cCMV not defined at all

Global development, n = 21

- Outcomes reported categorically
- Symptomatic cohort rates of global developmental delay ranged from 43% to 64%.
- 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

Fine motor, n=6

- 5 /6 studies found no difference between children with cCMV and uninfected controls.
- Predominantly comprised of children with asymptomatic cCMV, definitions of which varied by study.

Gross motor, n=8

- 7 studies comparison group of uninfected controls.[20,25,27,28,29,37,38]
- Studies reporting gross motor outcomes as “delayed milestones” or “mild motor delay” but no standardized measurement, not included
- Gross motor developmental delay in children with symptomatic cCMV (as defined by each study) ranged from 30-43%

Speech/language, n=8

- 6/8 studies found no differences in speech and language outcomes between children with cCMV and control groups
- Mostly asymptomatic cohorts
- 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.

Intellectual/cognitive, n=16

- Many measured IQ
- Studies that did not differentiate between symptomatic and asymptomatic cCMV largely reported average or typical range cognitive scores on standardized instruments, or scores that did not differ between children with cCMV and controls.

Intellectual/cognitive

- Symptomatic cCMV generally lower IQ than controls
- Several studies have found children with asymptomatic cCMV to have IQ scores no different than uninfected controls.

Other observations

- No study controlled for therapies/interventions
- Few controlled for other risk factors for DD
- Unclear if accommodations provided
- Hearing status not always reported
- Few studies followed children into adolescence

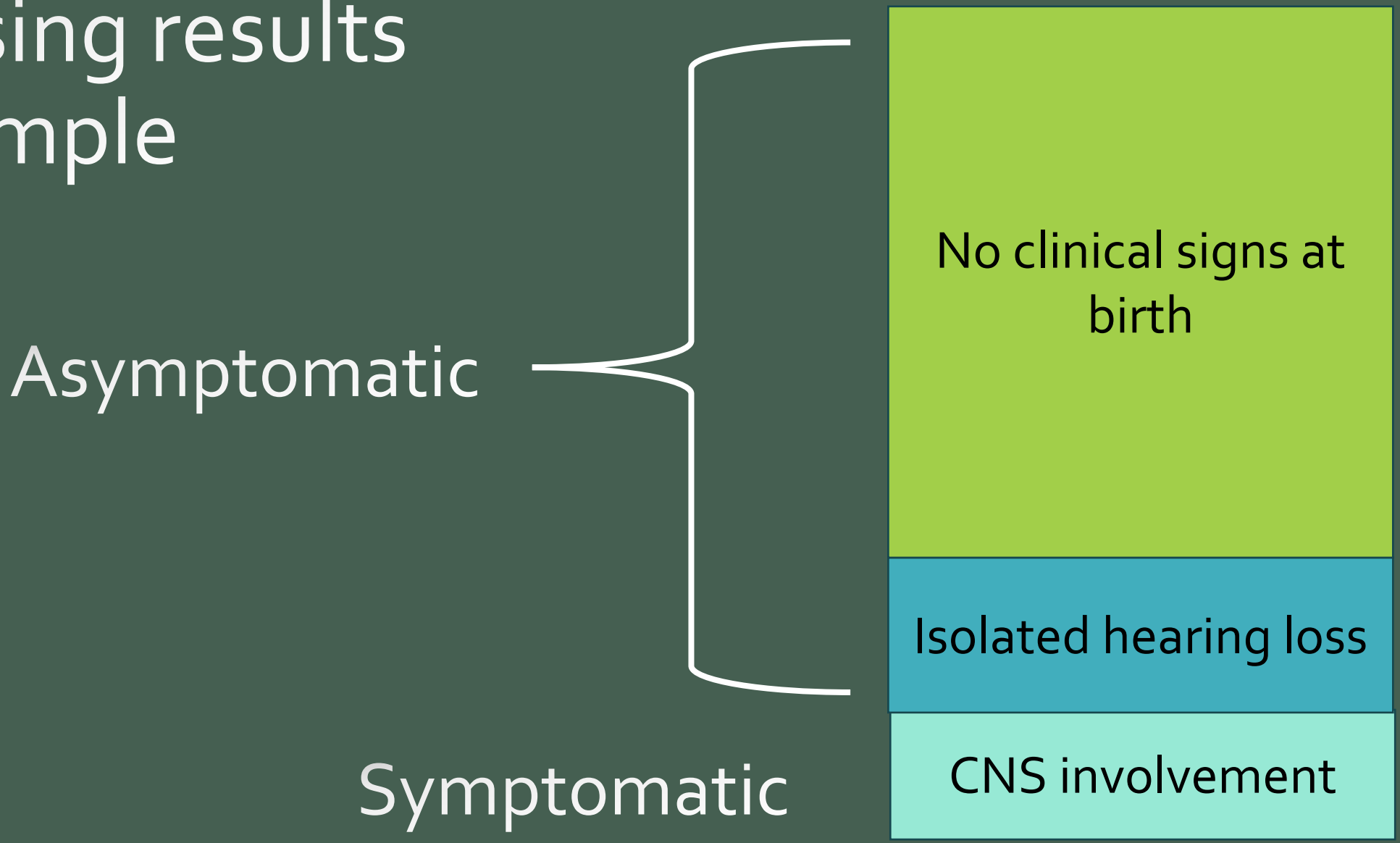
Discussion

Key findings

- Neurodevelopmental abnormalities were identified in a substantial number of children with cCMV, particularly in children with symptomatic cCMV
- Limited ability to draw more specific conclusions
- Definitions of disease severity varied widely prior 2017

Variation in definitions of cCMV severity may limit the generalizability of findings.

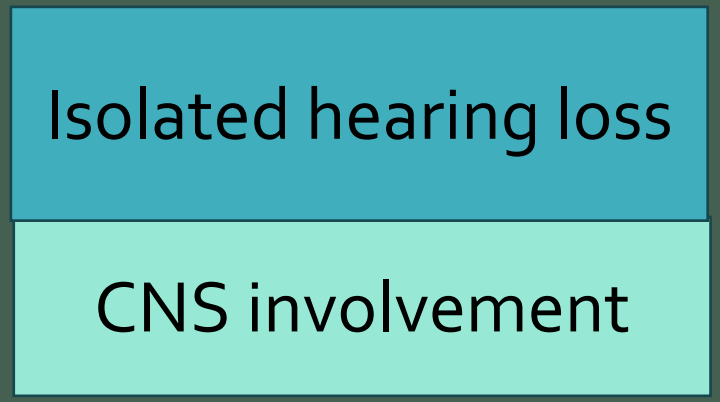
Biasing results example



Measuring speech outcomes

"Asymptomatic"

Biases asymptomatic scores upwards

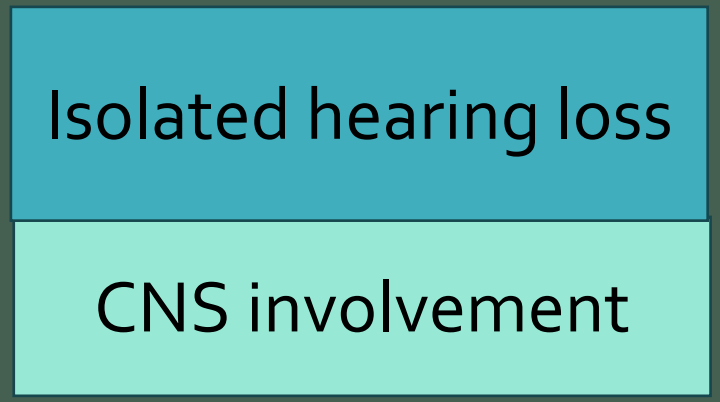


"Symptomatic"

Measuring speech outcomes

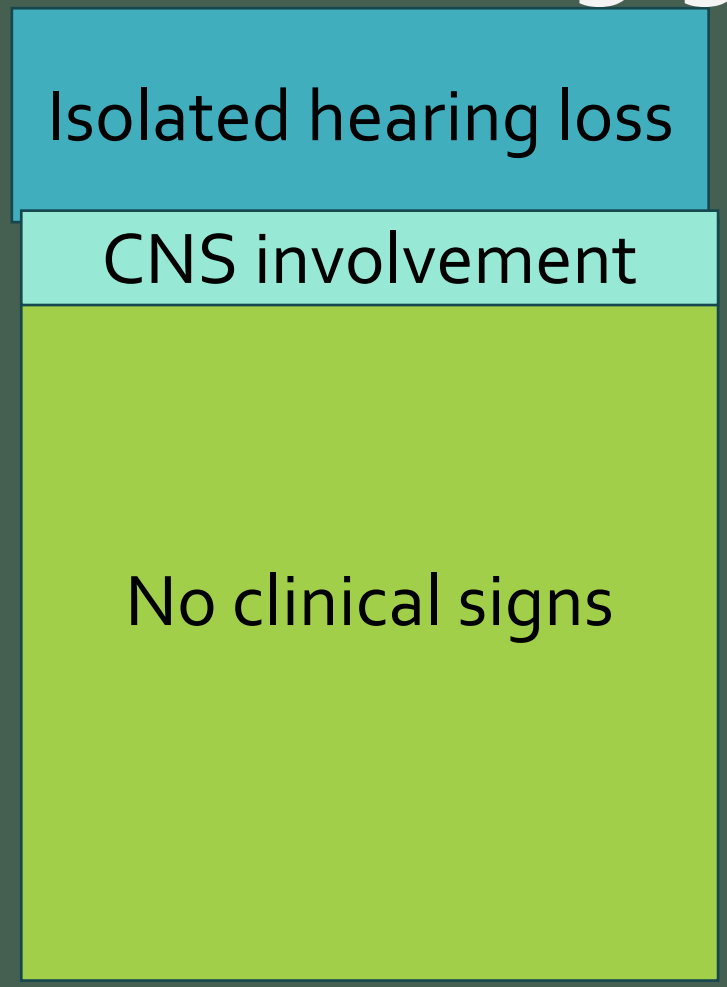
"Asymptomatic"

Biases asymptomatic scores upwards



"Symptomatic"

Measuring gross motor outcomes



Biases asymptomatic scores downwards

CNS involvement

"Asymptomatic"

"Symptomatic"

Key findings continued

- Validated instruments → categorical outcomes
- "Impairment" = huge category
- Significant differences but still in average range

Future studies

- 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.
- Nuanced measurements of outcomes