NICHD

NEONATAL RESEARCH NETWORK

Histologic Chorioamnionitis and Risk of Cerebral Palsy in Preterm Infants

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NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development

Disclosures

- Speaker: Viral G Jain

- Dr. Jain has no financial relationships to disclose or Conflicts of Interest to resolve. Any real or apparent conflicts of interest related to the content of this presentation have been resolved.

- This presentation will not involve discussion of unapproved or off-label, experimental, or investigational use of a drug.

Background – Cerebral Palsy

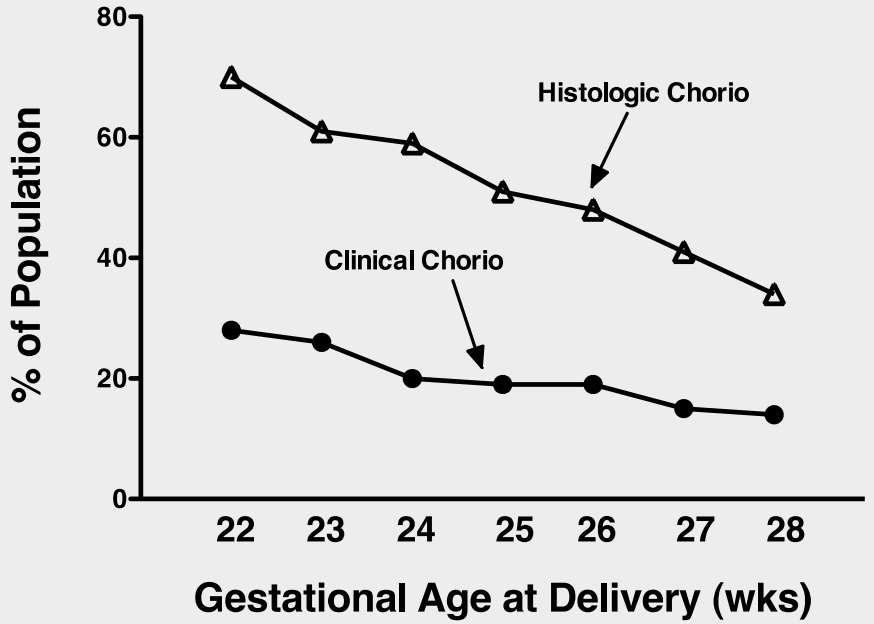
- Brain injuries in preterm infants manifest with neurodevelopmental impairments (NDI), including cerebral palsy (CP).
- CP affects ~9% of preterm infants born <32 weeks, increasing to 33% in those born ≤23 weeks. (Bell et al JAMA 2021)
- Rates of CP in the last decade steadily increasing in US. (DeMauro et al J Peds 2024).
- Children with all severity levels of CP are more likely to have cognitive development delays, multiple medical comorbidities, and poor growth.
- Cognitive impairment is the largest contributor to instability in NDI for a given infant over time, while CP remains relatively stable. (Taylor et al Pediatrics 2021)

Background - Chorioamnionitis

- Chorioamnionitis is an acute inflammation of the fetal membranes or the placenta, with or without infection
  - common cause of preterm birth (50-80%)
  - associated with neonatal mortality and significant morbidity
  - perinatal inflammation manifests with injuries leading to motor impairments

- The association of chorioamnionitis with CP has been inconclusive. (Jain et al Ped Res 2022)

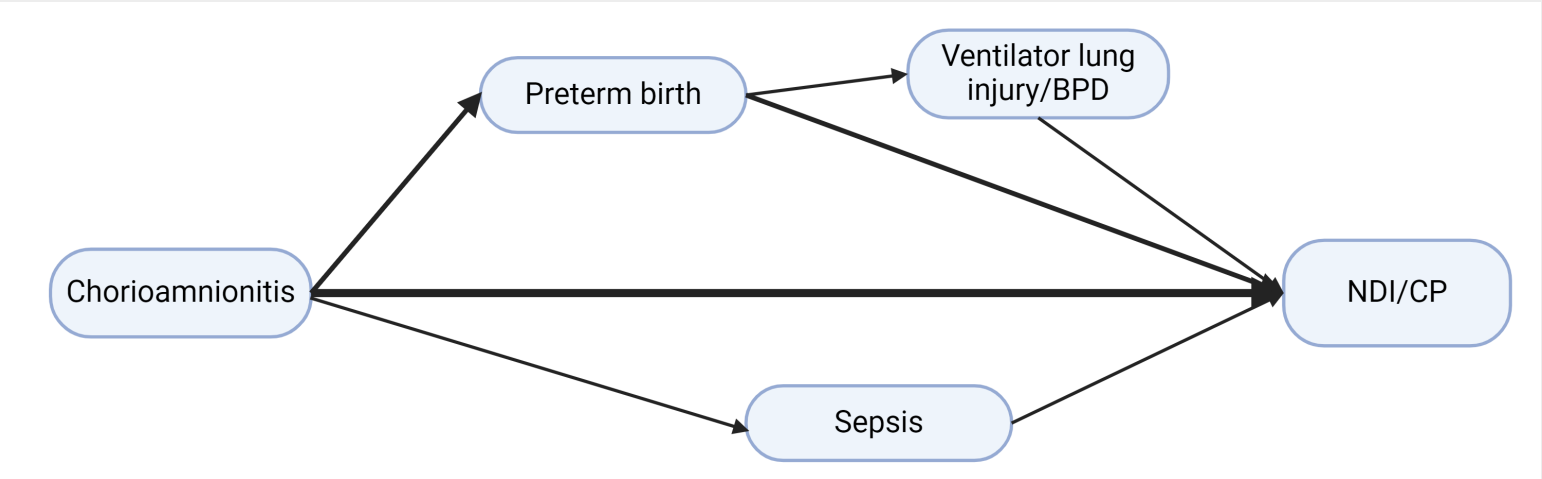
Chorioamnionitis in NICHD-NN Network for Infants Born at 22-28 wks GA - 2006-2007 (82% of Placentas Examined)



Stoll, et al., Pediatr, 2010

Background - Heterogeneous Outcomes

- Variations in the definition of chorioamnionitis (histological vs clinical)
- Mild chorioamnionitis has been shown to be neuroprotective in animal models and human studies. (Venkatesh, AJOG, 2020)
- Adjustment of variables that lie on the causal pathway (gestational age, ventilator days, sepsis)
- Varying definitions of CP



Hypothesis

Preterm infants <27 weeks' gestation exposed to histological chorioamnionitis (HCA) or funisitis (severe HCA) are more likely to die or develop CP compared to similar infants without exposure to HCA or funisitis.

Methods

- Inclusion:
  - Infants born alive at hospitals participating in the NICHD Neonatal Research Network (NRN) between 2012 - 2019 and at 22 $^{0/7}$ to 26 $^{6/7}$ gestation
    - Funisitis data from 2016 onwards

- Exclusion:
  - Outborn
  - No placental pathology performed
  - Congenital malformations and/or genetic syndromes
  - No active treatment after birth (intubation, surfactant therapy, respiratory support, chest compressions, epinephrine, volume resuscitation, blood pressure support, and/or parenteral nutrition)

Outcomes

- Primary outcome:
  - Composite outcomes of death or CP
    - defined by the Amiel-Tison standardized exam (per NRN definition) and Gross Motor Function Classification System (GMFCS) ≥1 at 22-26 months corrected age (CA)

- Secondary outcomes:
  - Components of the primary outcome (death and CP)
  - Death or moderate to severe NDI defined as the composite outcome of
    - BSID-III cognitive score of <85,
    - BSID-III motor score of <85,
    - CP diagnosis and GMFCS level ≥2,
    - bilateral blindness, and/or bilateral HI (no functional hearing with or without amplification)
  - Individual components of moderate-to-severe NDI.

Statistical Analysis

- Descriptive statistics used to summarize maternal and neonatal characteristics

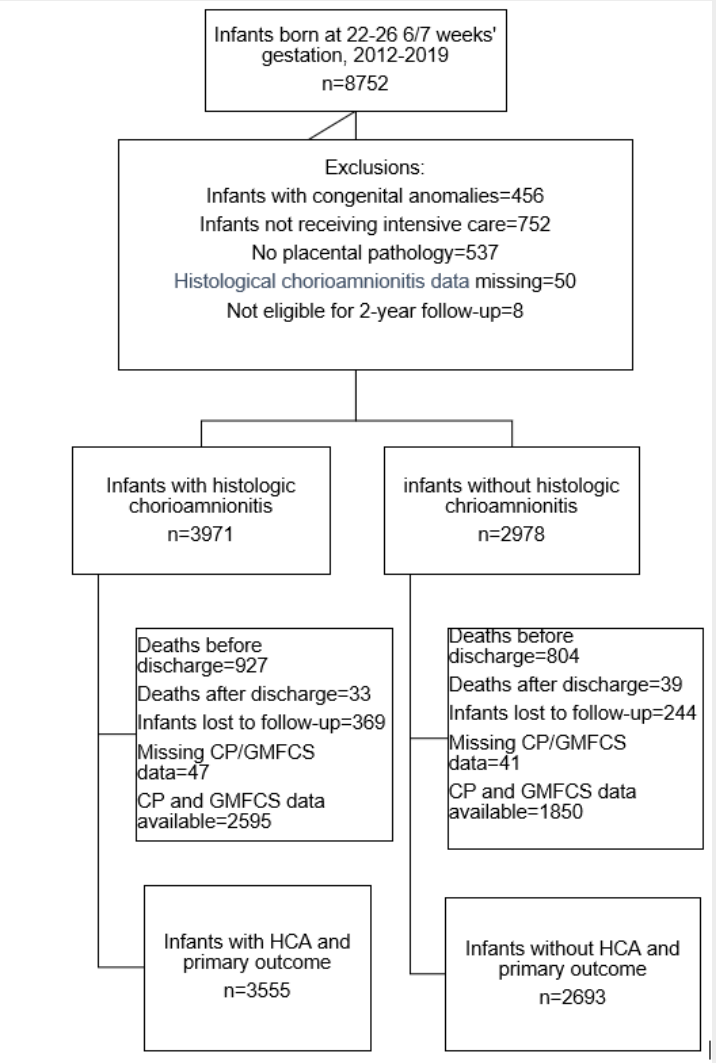
- Causal mediation analysis
  - As preterm birth lies on the causal pathway for CP, we investigated if gestational age indirectly mediated the relationship between HCA and the outcomes
  - Log-binomial regression models
  - Causal mediation was performed using the PROC CAUSALMED procedure in SAS (VanderWeele Annu Rev Public Health 2016)

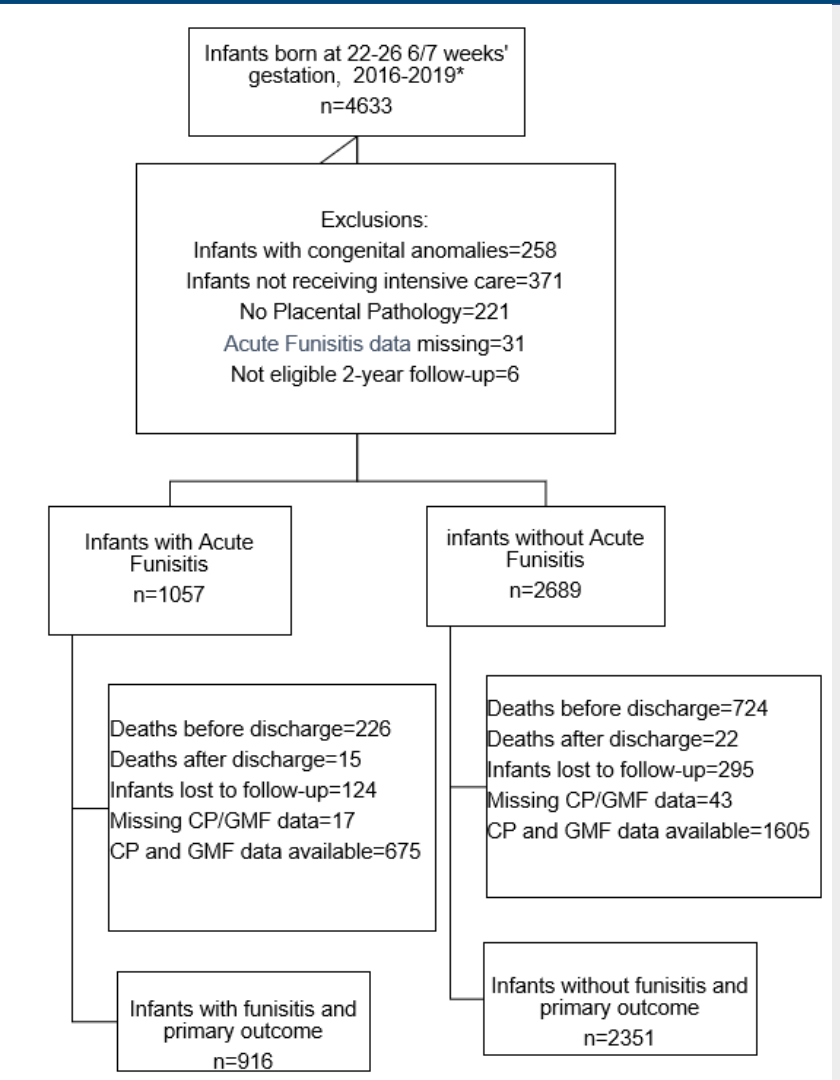
<u>Confounders:</u>

- maternal hypertension,
- antenatal steroids,
- magnesium sulfate,
- infant sex,
- maternal antibiotics,
- birth hospital,
- birth year,
- maternal education,
- maternal health,
- insurance status,
- birth weight z-score.

Results

- 93% - Placental pathology available
- Inclusion criteria met:
  - HCA - 8752 infants
  - Funisitis – 4633 infants
- 90% - had follow-up and complete CP data

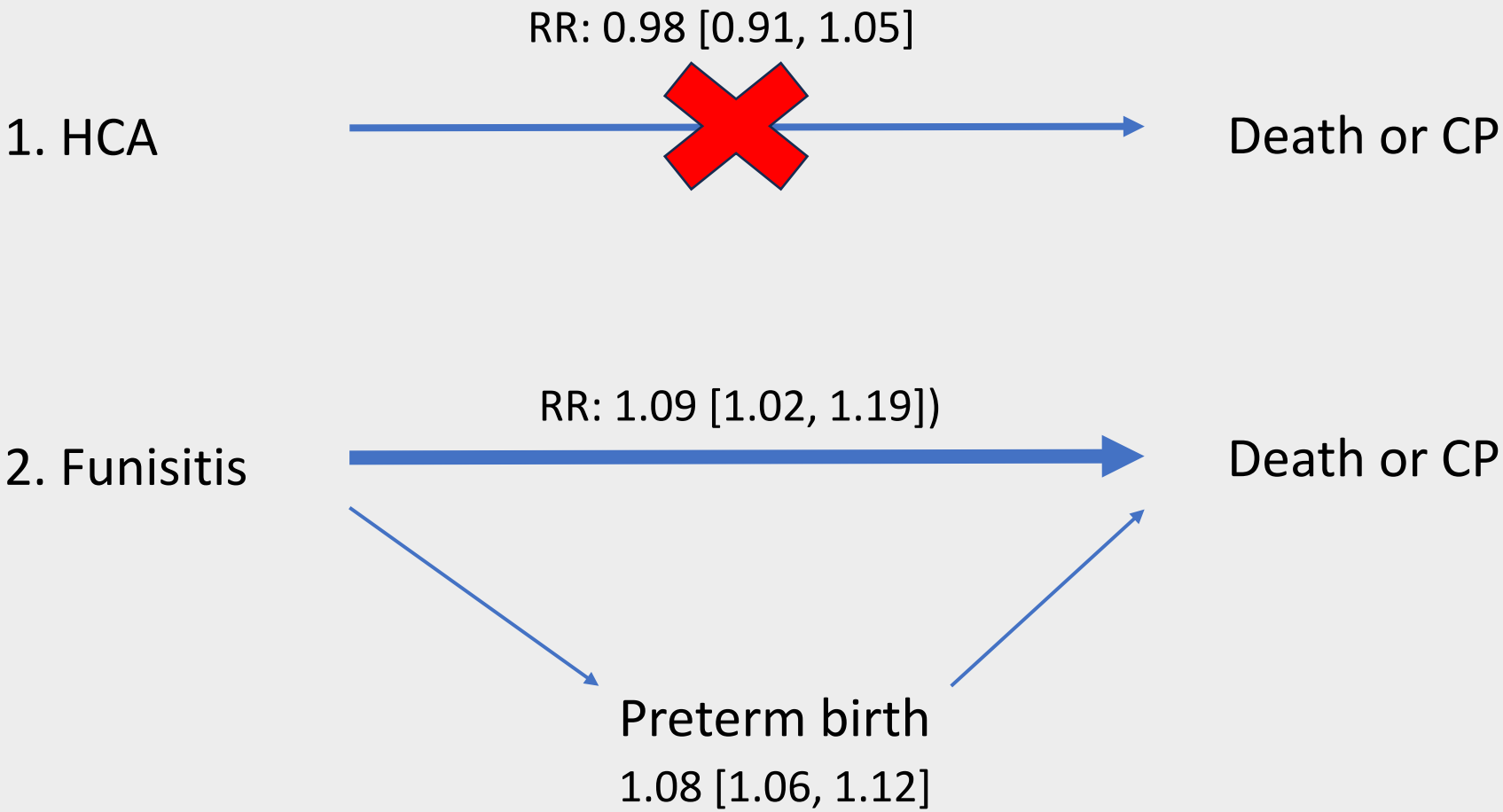




Results - Demographics

	No HCA (Controls) N=2978	HCA N=3971	P-value[β]	No Funisitis (Controls) N=2689	Acute Funisitis N=1057	P-value[β]
Maternal						
Hypertension (chronic/new), (%)	41.2	12.4	<0.001	31.3	11.7	<0.001
Antenatal steroids (%)	88.1	92.6	<0.001	90.7	94.2	<0.001
Magnesium sulfate, (%)	78.8	82.8	<0.001	82.8	84.3	0.29
Antenatal antibiotics, (%)	72.1	85.1	<0.001	77.0	86.8	<0.001
Neonatal						
Gestational age, median	25.4	25.0	<0.001	25.3	24.9	<0.001
Birth weight, median	690.0	725.0	<0.001	700.0	715.0	0.03
Sex, (%)	52.8	50.2	0.03	53.0	45.5	<0.001
SGA, (%)	16.0	2.60	<0.001	11.0	1.90	<0.001

Results – Primary Outcome (Multivariable)

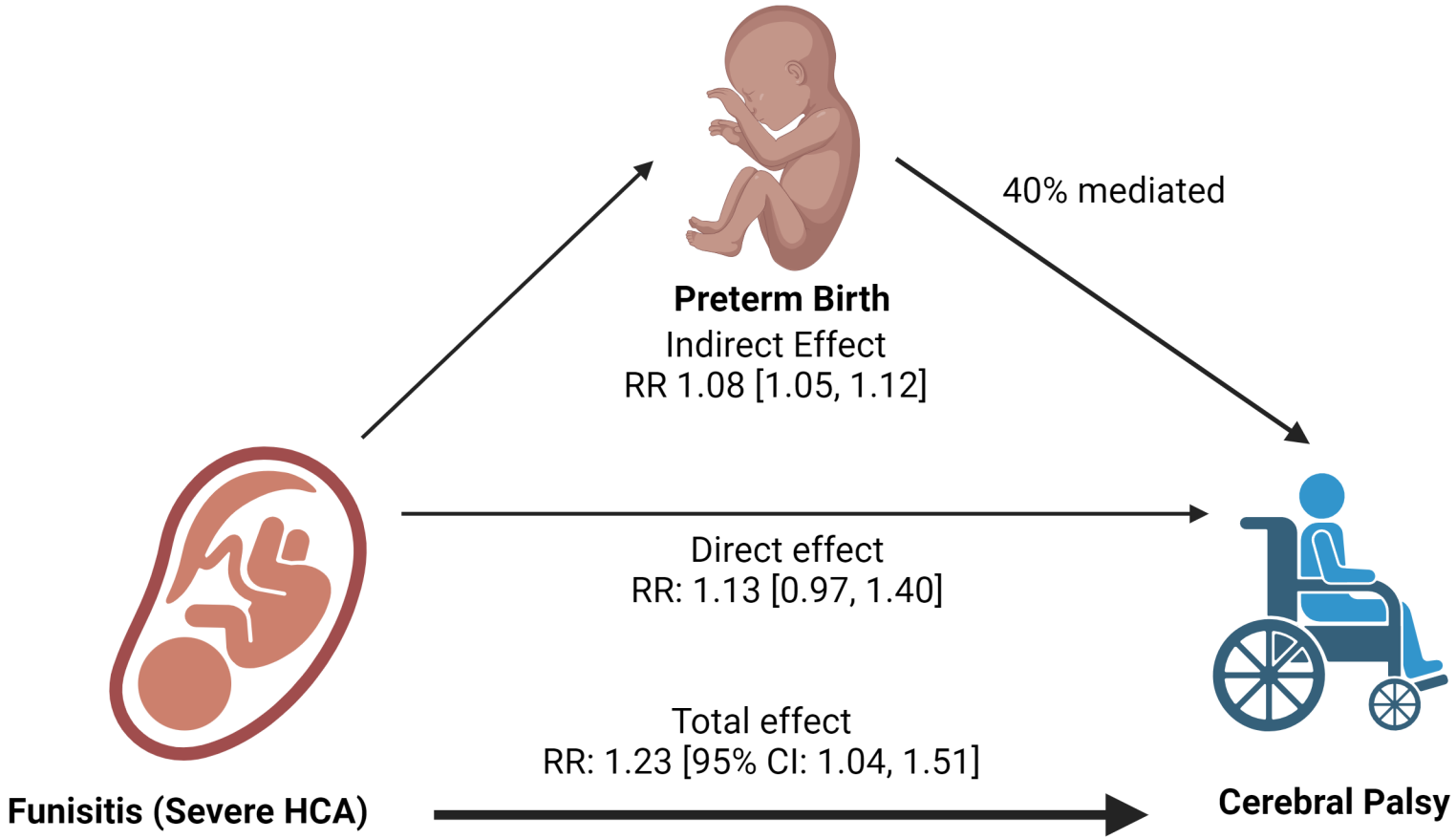


Results – Secondary Outcome (Multivariable)

- HCA **was** associated with a lower risk of death (RR: 0.89 [0.82, 0.98])
  - No association was observed for CP, death or NDI, NDI, and any of its components

- Funisitis **was** associated with a lower risk of death (RR: 0.71 [0.61, 0.81])
- Funisitis **was** associated with a higher risk of CP (RR: 1.23 [95% CI: 1.04, 1.51])
  - No differences were seen for death or NDI, NDI, and any of its components

Results - Mediation Analysis



Strengths

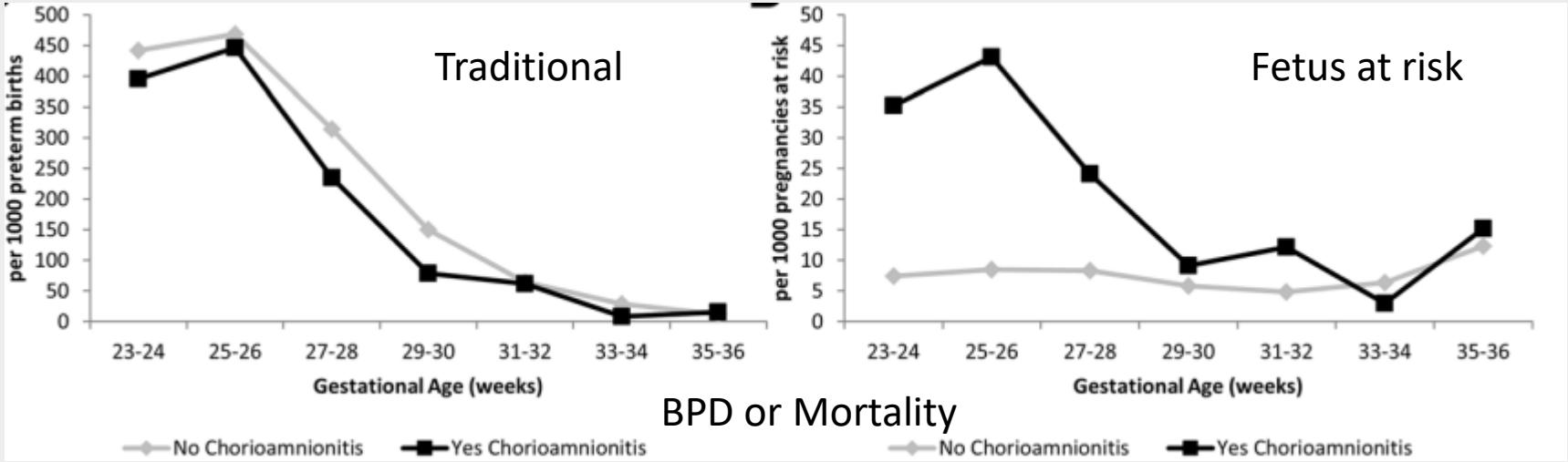
- Largest multi-center study evaluating HCA and CP, larger than a recent meta-analysis. (Shiz, Pediatrics, 2017)
  - detect a difference in the risk of death or CP with funisitis exposure
  - independent contribution of early preterm birth in the causality of CP

- Placental pathology available for 94% of the infants.

- Follow-up data available for 90% of all eligible infants.

Limitation – Selection Bias and Fetus-at-risk approach

- Paradoxical lower risk of death in infants exposed to HCA or funisitis.
- Selection Bias:
  - Excluded infants not receiving active intervention
  - No data on stillbirth
  - Limited to <27 weeks gestation
  - Fetus at risk: All live births and stillbirths at a given GA and beyond are to be used as the denominator (Joseph/Kramer AOGS 2017)



BPD or Mortality

Metcalfe et al BMC Ped 2017

Conclusion

- In this large multicenter study of extremely preterm infants, HCA did not increase the combined outcome of death or CP.
- Higher risk of death or CP was seen in funisitis-exposed preterm infants,
  - primarily mediated by earlier preterm birth.
- An increased risk of CP was seen in surviving infants exposed to funisitis/severe HCA,
  - approximately half of the effect appeared to be a direct adverse effect on CP
- Given the increased risk of sepsis, BPD, IVH, and CP after exposure to HCA, future research on immune dysfunction and neuroinflammation related to HCA may improve neurodevelopmental outcomes of preterm infants.

Neonatal Research Network Centers (2011-2019)

- Brown University
- Case Western Reserve University
- Children's Mercy Hospitals and Clinics, University of Missouri-Kansas City
- Cincinnati Children's Medical Center
- Duke University
- Emory University
- Indiana University
- Nationwide Children's Hospital, Ohio State University
- RTI International
- Stanford University
- University of Alabama at Birmingham
- University of California – Los Angeles
- University of Iowa
- University of New Mexico
- University of Pennsylvania
- University of Rochester
- University of Texas Southwestern
- University of Texas Health Science Center at Houston
- Wayne State University
- University of Utah