



# Characterizing Clinical Manifestations of Congenital Zika Syndrome in Non-Microcephalic Infants



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## Background

- Zika Virus (ZIKV) is a mosquito-borne virus that has been linked to adverse fetal/neonatal outcomes through vertical transmission
- Antenatal ZIKV exposure is known to cause microcephaly and serious brain anomalies, but the full spectrum of abnormalities have not been delineated.

## Objective

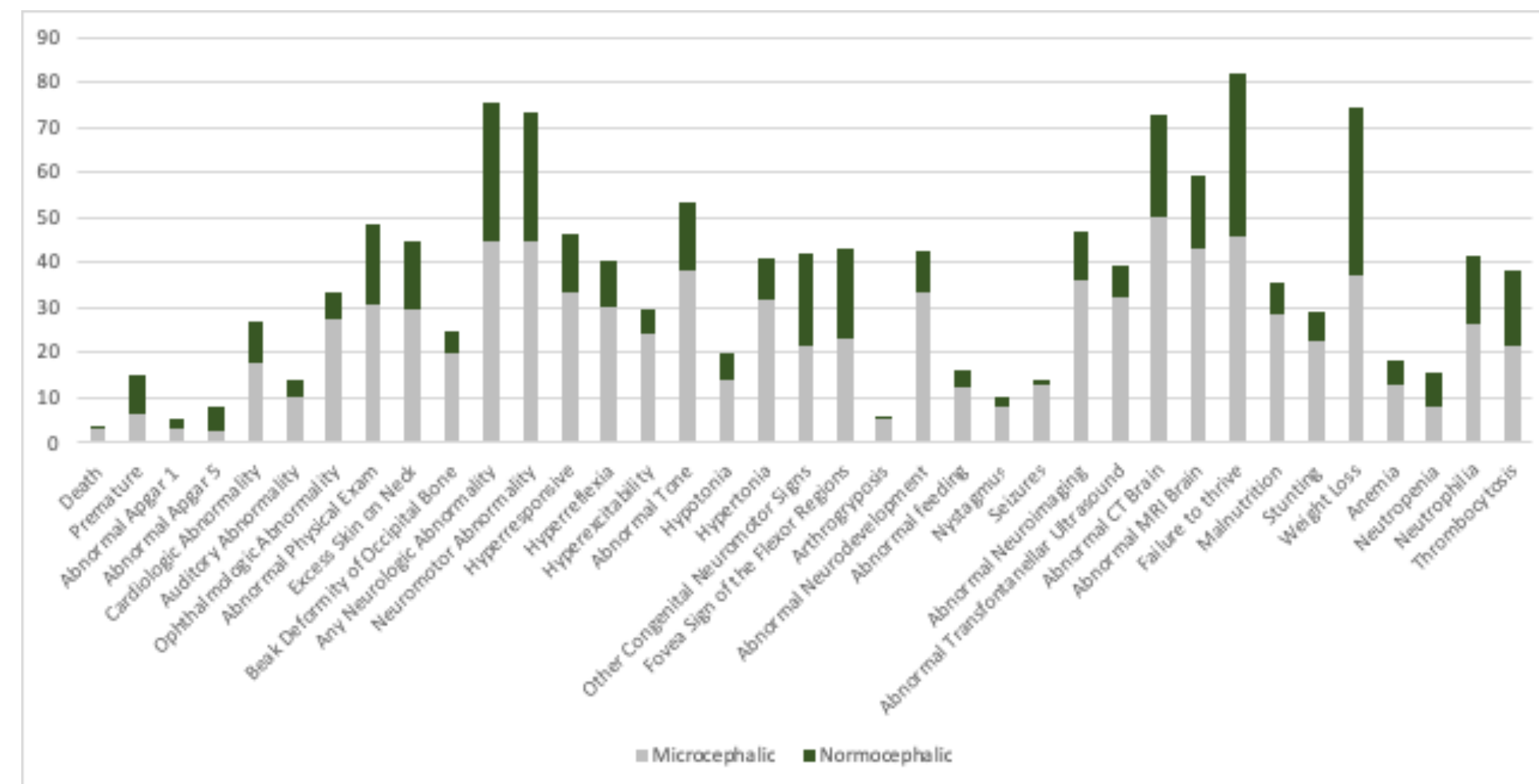
- To characterize the structural anomalies, central nervous system malformations, and neurocognitive disabilities associated with Congenital Zika Syndrome (CZS) we analyzed the clinical manifestations in infants from Rio de Janeiro, Brazil who were exposed to ZIKV in utero.

## Methods

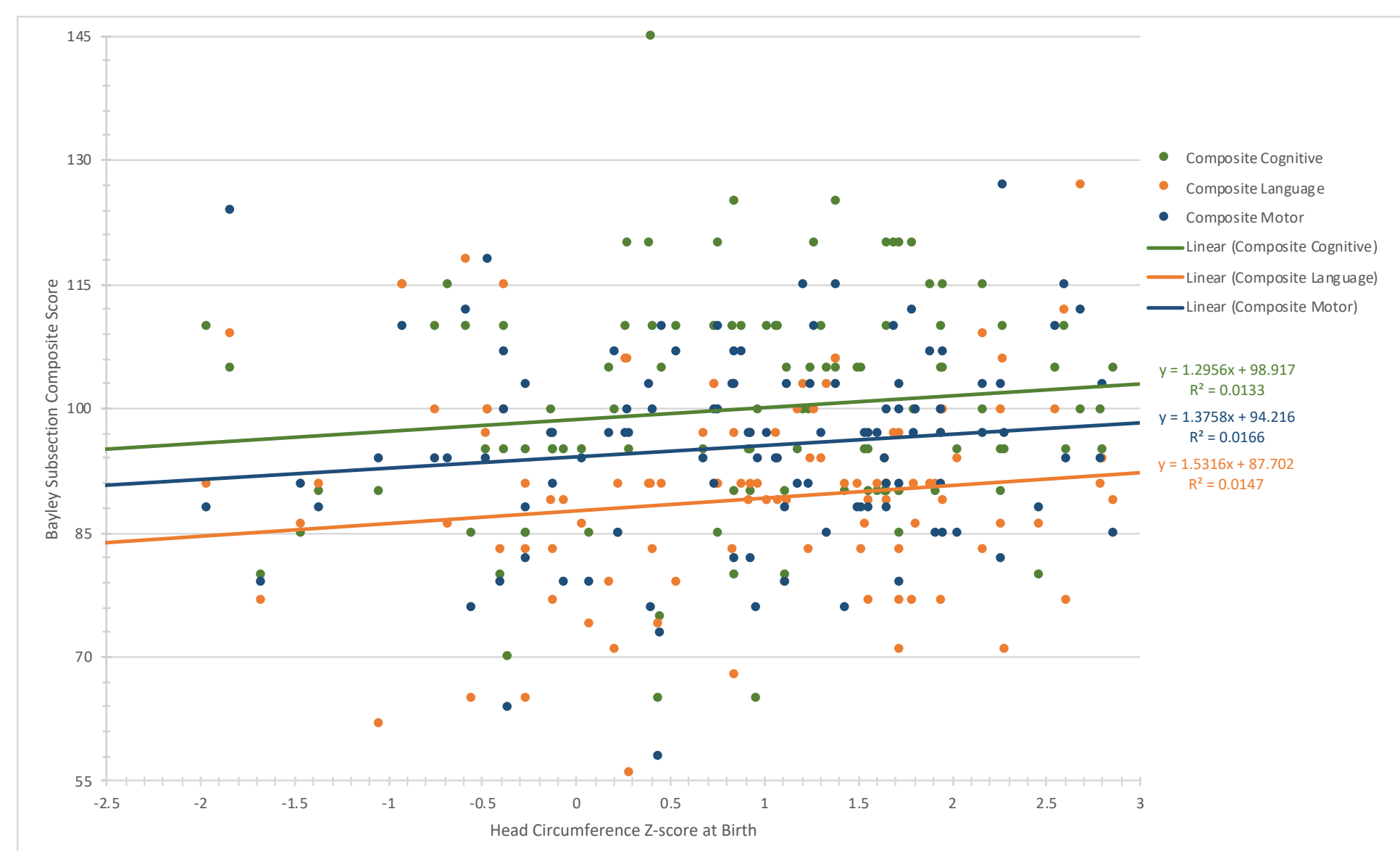
- Pregnant women who presented with febrile illness and concurrent rash during the ZIKV outbreak were enrolled
- Their offspring were followed prospectively for 3 years at Instituto Fernandes Figueira/FIOCRUZ
- Vertical exposure to ZIKV was determined by maternal or neonatal PCR or IgM serology
- Bayley-III Scales of Infant and Toddler Development was used for individuals >6 months to assess neurodevelopment
- The mean score of Bayley-III is 100 with a standard deviation of  $\pm 15$ . A score  $\leq 85$  indicates at risk of developmental delay and a score  $\leq 70$  indicates severe developmental delay
- Statistical analysis was performed using SPSS

## Results

Variable	Microcephalic Infants (N = 53)	Normocephalic Infants (N = 161)	All Infants (N = 219)
no. of infants/total no. (%)			
Death	4/52 (7.7)	2/160 (1.3)	8/217 (3.7)
Premature	6/53 (11.3)	27/161 (16.8)	33/216 (15.3)
Average Weight Z-score at Birth	-1.3	0.14	-0.21
Average Head Circumference Z-score at Birth	-3.56	0.84	-0.25
Average Height Z-score at Birth	-1.09	0.08	-0.22
Failure to thrive	46/47 (97.9)	109/142 (76.8)	156/190 (82.1)
Malnutrition	38/46 (82.6)	28/138 (20.3)	66/185 (35.7)
Stunting	30/47 (63.8)	25/142 (17.6)	55/190 (29.0)
Weight Loss	34/46 (73.9)	102/138 (73.9)	137/185 (74.1)
Cardiologic Abnormality	19/46 (41.3)	20/100 (20.0)	39/146 (26.7)
Auditory Abnormality	13/50 (26.0)	14/141 (9.9)	27/192 (14.0)
Ophthalmologic Abnormality	42/53 (79.3)	28/158 (17.7)	71/213 (33.3)
Abnormal Physical Exam	16/22 (72.7)	39/93 (41.9)	56/116 (48.3)
Excess Skin on Neck	16/22 (72.7)	35/93 (36.6)	52/116 (44.8)
Beak Deformity of Occipital Bone	14/22 (63.6)	15/93 (16.1)	29/116 (25.0)
Neurologic Abnormalities	52/53 (98.1)	109/160 (68.1)	162/215 (75.4)
Neuromotor Abnormality	46/46 (100.0)	89/139 (64.0)	136/186 (73.1)
Hyperresponsive	39/46 (84.8)	45/137 (32.9)	85/184 (46.2)
Hyperreflexia	37/46 (80.4)	36/136 (26.5)	74/183 (40.4)
Hyperexcitability	32/46 (69.6)	21/137 (15.3)	54/184 (29.4)
Abnormal Tone	45/46 (97.8)	53/137 (38.7)	98/184 (53.3)
Hypotonia	16/46 (34.8)	21/137 (15.3)	37/184 (20.1)
Hypertonia	10/46 (21.7)	35/137 (25.6)	45/184 (24.5)
Other Congenital Neuromotor Signs	10/23 (43.5)	39/93 (41.9)	49/117 (41.9)
Fovea Sign of the Flexor Regions	10/20 (50.0)	39/93 (41.9)	49/114 (43.0)
Arthrogryposis	5/23 (21.7)	2/93 (2.2)	7/117 (6.0)
Abnormal Neurodevelopment	42/46 (91.3)	28/115 (24.4)	78/183 (42.6)
Abnormal feeding	16/47 (34.0)	15/143 (10.5)	31/191 (16.2)
Nystagmus	5/26 (19.2)	3/51 (5.9)	8/78 (10.3)
Seizures	21/46 (46.7)	5/137 (3.7)	26/184 (14.1)
Abnormal Neuroimaging	51/53 (96.2)	44/149 (29.5)	95/203 (46.8)
Abnormal Transfontanelar US	44/46 (95.7)	30/141 (21.3)	74/188 (39.4)
Abnormal CT Brain	50/50 (100.0)	23/50 (46.0)	73/100 (73.0)
Abnormal MRI Brain	23/23 (100.0)	16/43 (37.2)	39/66 (59.1)
Anemia	8/29 (27.6)	5/45 (11.1)	14/76 (18.4)
Neutropenia	5/29 (17.2)	7/45 (15.6)	12/76 (15.8)
Neutrophilia	16/30 (53.3)	14/45 (31.1)	32/77 (41.6)
Thrombocytosis	13/29 (44.8)	16/45 (35.6)	29/76 (38.2)
Thrombocytopenia	3/29 (10.3)	5/45 (11.1)	9/76 (11.8)



**Figure 1. Frequency of Adverse Exam Findings in Zika Exposed Infants, Microcephalic vs. Non-Microcephalic**  
Adverse outcome frequencies describing the entire ZIKV positive population (N= 219) are demonstrated. Frequency comparison between microcephalic outcomes (N=53, grey) and non-microcephalic outcomes (N=112, green) are demonstrated as proportions.



**Figure 2. Individual Scores on the Bayley-III Scales According to Head Circumference Z-score at Birth**  
Shown are the scores for cognitive (green), language (orange), and motor (blue) functions on the Bayley-III Scales. The scores of 112 non-microcephalic children between the ages of 6 months and 3 years are indicated by circles. Head circumference was measured at birth and converted to Z-scores based on INTERGROWTH-21<sup>st</sup> Project data for gestational age and sex.

- The study enrolled 296 pregnant women
- In utero exposure to ZIKV was confirmed in 219 cases
- 53 had congenital microcephaly
- Among the non-microcephalic infants, the majority had failure to thrive (FTT), mainly due to weight loss (deceleration of growth across 2 percentiles)
- The majority of infants had a neurologic abnormality (68.1%)
- All abnormal findings are more prevalent in microcephalic infants.
- Among non-microcephalic infants with Bayley III exam scores (N=112), head circumference was a significant indicator of abnormal cognitive (p=0.004) and developmentally delayed language score (p=0.011) (Figure 2)

## Conclusions

- Infants with CZS without microcephaly suffer from congenital symptoms similar to those with microcephaly but less frequently
- Infant head circumference z-score at birth of non-microcephalic infants is significantly associated with neurocognitive development
- Recognition of the myriad of CZS phenotypes and spectrum of severity, beyond microcephaly, can help ensure early intervention, appropriate cross-disciplinary evaluation and comprehensive therapeutic care

## References

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