Zika Microcephaly Cutoffs Revisited: Nonparametric Methods in Fetal Growth

Jayson D. Wilbur, 1 Eric Ohuma, 2 Luo Xiao, 3 Samer Mouksassi, 4 Ryan Hafen, 5 Representing the Healthy Birth, Growth, and Development knowledge integration (HBGDk) Community 6

1 Metrum Research Group, Tariffville, CT, USA; 2 University of Oxford, Oxford, UK; 3 North Carolina State University, Raleigh, NC, USA; 4 Certara, Montreal, QC, Canada; 5 Hafen Consulting, Seattle, WA, USA; 6 Bill & Melinda Gates Foundation, Seattle, WA, USA

Objectives

- An increase in the number of microcephaly cases in Brazil has been associated with exposure to Zika virus.
- Screening thresholds for microcephaly have been published in terms of newborn head circumference. 1
- We evaluated these criteria based on modeling of data about:
  - Longitudinal fetal growth trajectories.
  - Newborn size.

Methods

Functional Principal Component Analysis (FPCA) 2 was used to model head circumference growth trajectories using nonparametric functions to characterize:

- Mean trajectory
- Subject-level random effects

\[
Y(t) = \mu(t) + X(t) + \varepsilon(t)
\]

\[
Y(t) = \mu(t) + \sum_{i=1}^{k} z_i \phi_i(t) + \varepsilon(t)
\]

\[
Cov(X(s),X(t)) = \sum_{i=1}^{k} \lambda_i \phi_i(s) \phi_i(t)
\]

\[
\varepsilon_i \text{ i.i.d. } N(0,\sigma^2)
\]

\[
z_i \text{ i.i.d. } N(0,\lambda_i)
\]

Estimated covariance function based on fetal ultrasound data.

Principal eigenfunctions derived from the covariance function that are orthogonal functions characterizing fetal growth phenotypes.

Abbreviation: FPC, functional principal component.

Results

- Microcephaly thresholds that did not account for gestational age ignored an important source of biological variation.
- Factors associated with maternal health also contributed to population and subject-level deviations from international standards, which accounted for gestational age. 3

Conclusions

- Establishing fixed cutoffs for microcephaly in terms of newborn head circumference size ignores important sources of variation.
- This variation can be accounted for using a model-based approach.

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