HEALTHY BIRTH, GROWTH & DEVELOPMENT

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 (HBGD*ki*) 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

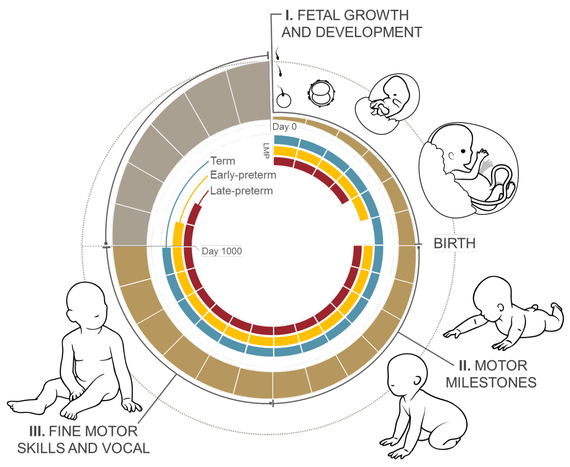


Fig. 1 Healthy Birth Growth and Development Lifecycle diagram.

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**

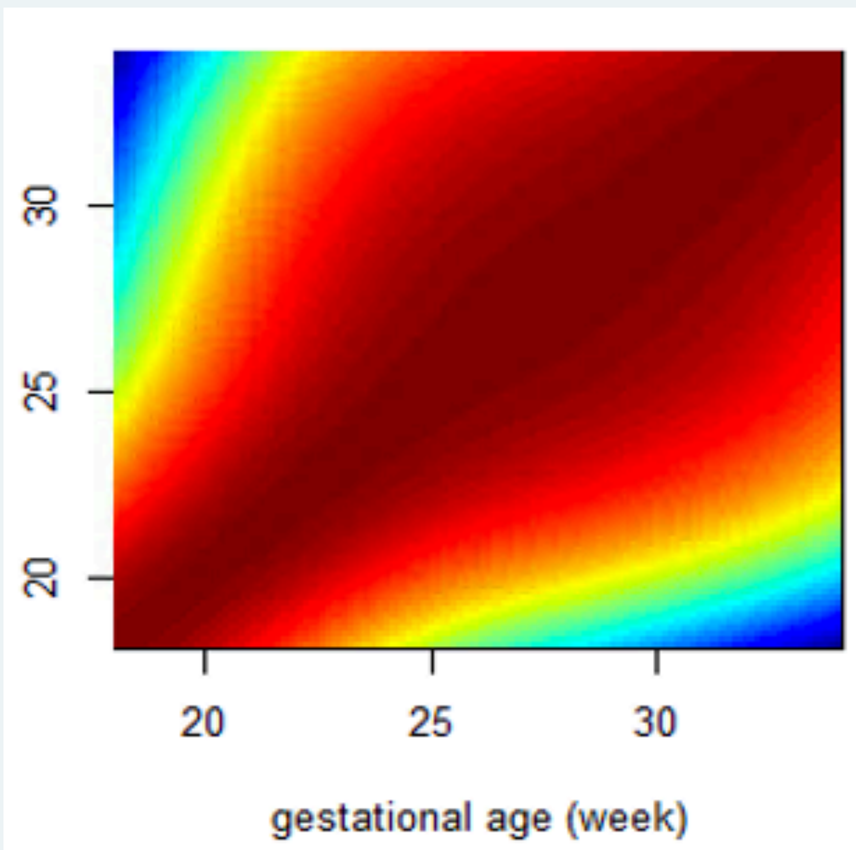
$$Y_i(t) = \mu(t) + X_i(t) + \varepsilon_i(t)$$

$$Y_i(t_{ij}) = \mu(t_{ij}) + \sum_{k=1}^{r} \xi_{ik}\varphi_k(t_{ij}) + \varepsilon_{ij}$$

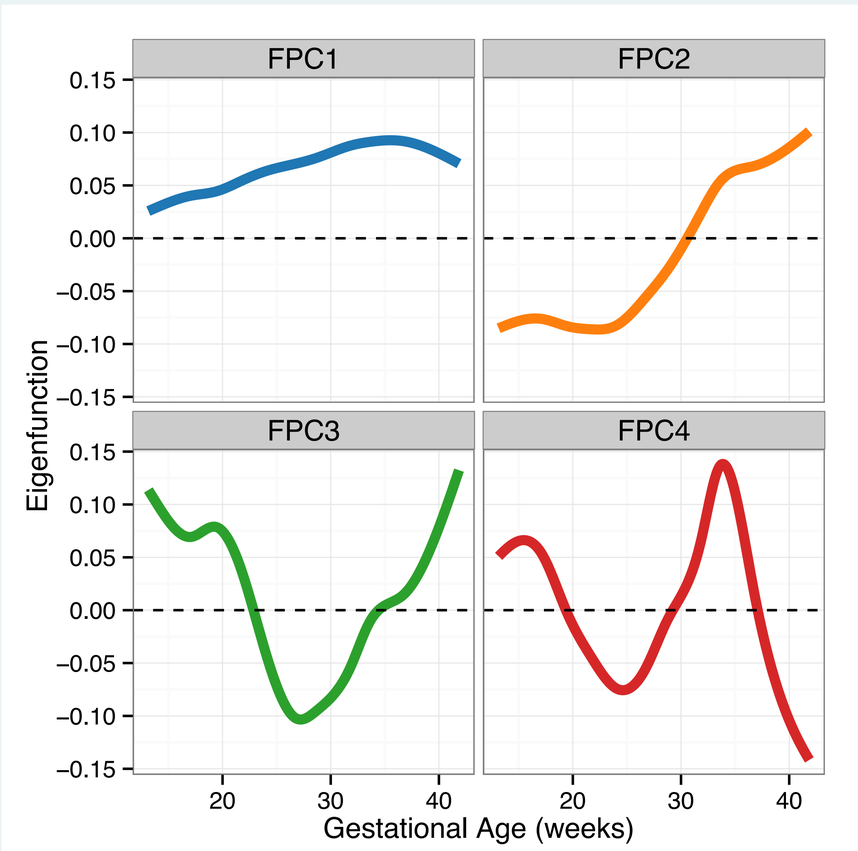
$$Cov(X_i(s), X_i(t)) = \sum_{k=1}^{r} \lambda_k \varphi_k(s)\varphi_k(t)$$

$$\varepsilon_{ij} \; i.i.d. \; N(0, \sigma^2)$$

$$\xi_{ik} \; i.i.d. \; N(0, \lambda_k)$$



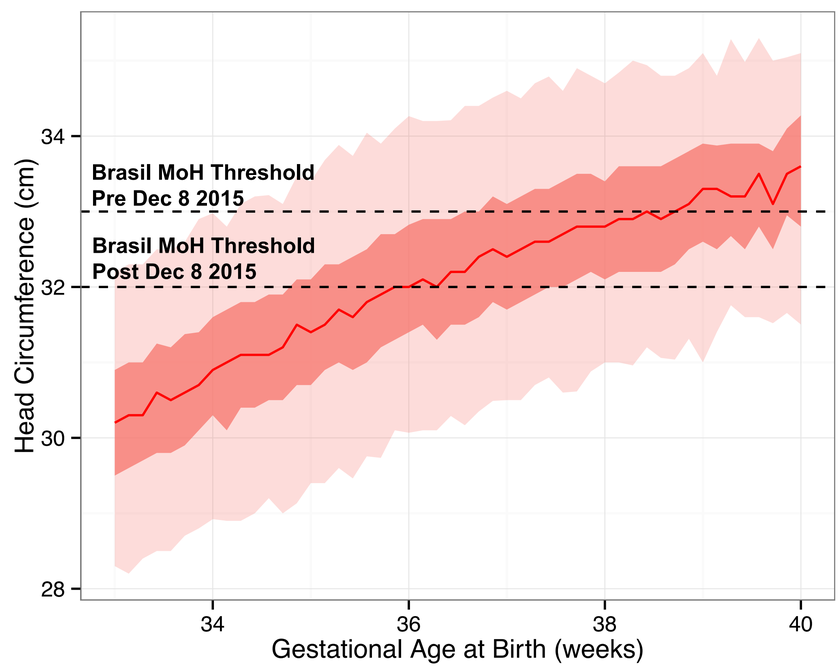
Estimated covariance function based on fetal ultrasound data.



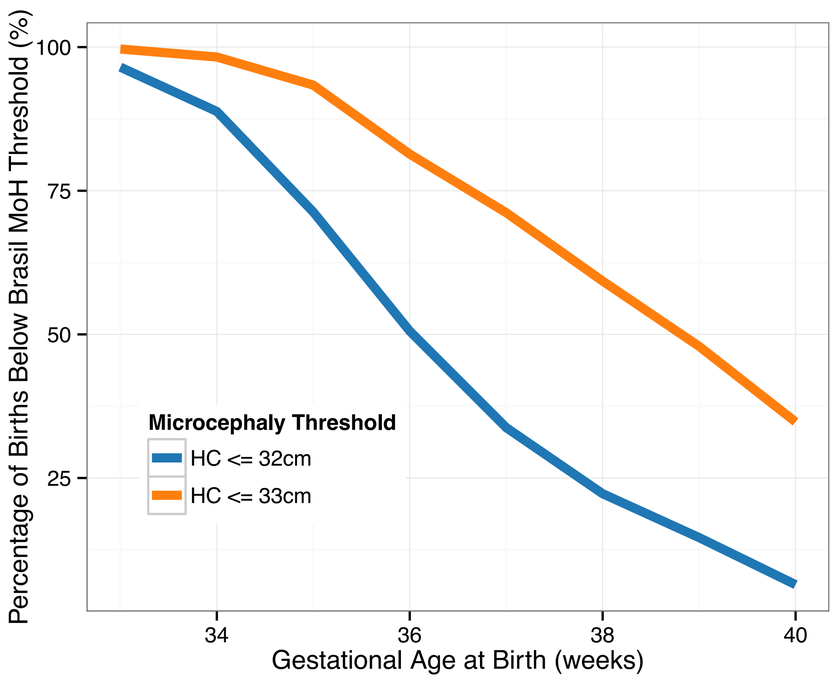
Principal eigenfunctions derived from the covariance function that are orthogonal functions characterizing fetal growth phenotypes.
Abbreviation: FPC, functional principal component.

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]**



Relation between head circumference and gestational age at birth.



Relation between births below Zika threshold and gestational age at birth.

References

1. Victora CG, et al. Microcephaly in Brazil: how to interpret reported numbers? *Lancet*. 2016;387(10019):621-624.
2. Xiao L, et al. Fast covariance estimation for high-dimensional functional data. *Stat Comput.* 2016;26(1):409-421.
3. Villar J, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. *Lancet.* 2014;384(9946): 857-868.

Sponsored by the Healthy Birth, Growth, and Development (HBGD) initiative representing Discovery & Translational Sciences, Integrated Development, Integrated Delivery, Nutrition, Agriculture, Water, Sanitation & Hygiene, Maternal, Newborn & Child Health, Enteric & Diarrheal Diseases, and Pneumonia Program Strategy Teams. HBGD*ki* was conceived of and is directed by shasha.jumbe@gatesfoundation.org.

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.**

Acknowledgment

Sponsored by the Bill & Melinda Gates Foundation, Healthy Birth, Growth, and Development initiative.